INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

The present invention relates to compounds which inhibit dipeptidyl peptidase IV (DPP-IV) activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, methods for the treatment of disease states associated with DPP-IV activity, to their use as medicaments and to their use in the manufacture of medicaments for use in the inhibition of DPP-IV in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of diabetes mellitus in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of diabetes mellitus in warm-blooded animals such as humans.

DPP-IV is a serine protease found throughout the body, which degrades and regulates the activity of several regulatory peptides in man including glucagon-like peptide-1 (GLP-1), GLP-2, GHRH (growth hormone releasing hormone) and GIP (glucagon interacting peptide). GLP-1 is a peptide hormone which is released from the intestinal tract wall into the bloodstream in response to a meal and strongly influences post-prandial glucose metabolism. As post-prandial glucose levels rise, GLP-1 acts directly on pancreatic β-cells to augment insulin release and also promote new insulin biosynthesis. Simultaneously, GLP-1 delays gastric emptying, further suppressing meal-related rise in plasma glucose. It has been shown (Rachman, J. et al, (1997), *Diabetologia*, **40**, 205-211; Nauck, M.A. et al, (1996), *Diabetologia*, **39**, 1546-1553; Gutniak, M.K. et al, (1994), *Diabetes Care*, **17**, 1039-1045; Rachman J. et al, (1996) *Diabetes*, **45**, 1524-1530) that GLP-1 administration either subcutaneously or by intravenous infusion improves glucose tolerance in diabetic patients, however daily administration of GLP-1 is not generally considered to be a desirable form of therapy.

DPP-IV degrades GLP-1 circulating in the bloodstream and inhibition of DPP-IV activity causes an increase in the half life, and therefore activity, of GLP-1. Additionally DPP-IV inhibitors have beneficial effects on pancreatic failure: Ribel U. et al ((2001) Diabetologia, 44, A192, 738) described how the DPP-IV inhibitor valine pyrrolidide (VP) promoted differentiation of new beta cells in 60% pancreatectomised rats. Therefore, administration of a DPP-IV inhibitor should result in prolongation of endogenous GLP-1 activity and thus potentially in a clinically significant lowering of diabetic hyperglycemia. A DPP-IV inhibitor may potentially be useful for the prevention, delay or treatment of Type 2 (non-insulin

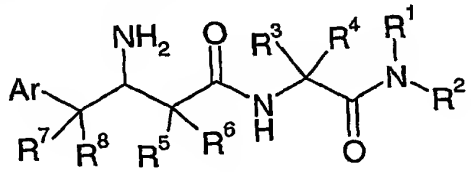
dependent) diabetes mellitus.

Novel DPP-IV inhibitors have been described in the art. Many are 2-cyanopyrrolidines derivatives with a significant range of substituents bonded to the ring nitrogen (see for example WO 98/19998, WO 00/34241, WO 01/96295, WO 01/40180), or contain this structure (see for example WO 01/68603 which discloses cyclopropyl fused cyano pyrrolidines). Others are cyanothiazolidines (see for example US 6110949, US 6107317, WO 99/61431), also with a variety of substituents bonded to the ring nitrogen. Still others contain pyrrolidine, piperidine, or morpholine rings which may contain substituents on the ring carbon atoms other than cyano groups (see for example WO 03/000181 and WO 03/000180).

We have surprisingly found a new structural class of DPP-IV inhibitors.

Accordingly, the present invention provides a compound of formula (I)

or a pharmaceutically-acceptable salt thereof,



(I)

wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl,

-(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl, -(1-6C)alkylSO$_2$NH(1-6C)alkyl, -(1-6C)alkylSO$_2$ (1-6C)alkyl, -SO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$N-di(1-6C)alkyl;

or

R^1 and R^2 may together with the nitrogen to which they are attached form a ring defined by HET1 or HET3; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO$_2$(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, (5-12C)bicycloalkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, AR1, AR2, HET1, HET2, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

wherein any (1-6C)alkyl group within any definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7 or R^8 is optionally substituted by 1 or 2 substituents independently selected from hydroxy and fluoro;

wherein any (3-8C)cycloalkyl, (3-8C)cycloalkenyl, (5-12C)bicycloalkyl or (6-12C)tricycloalkyl within any definition of R^2, R^3 or R^4 is optionally substituted;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

HET3 is an N-linked saturated bicyclic or tricyclic ring system, containing up to 12 ring atoms including the linking nitrogen atom;

wherein suitable optional substituents on (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from phenyl (optionally substituted with halo, trifluoromethyl, (1-4C)alkyl or (1-4C)alkoxy)), halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -SO_2(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl, -SO_2Ndi(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl.

A further embodiment of the invention comprises a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, –(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1–6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO_2(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl, and -(1-6C)alkylSO_2N-di(1-6C)alkyl;

or

R^1 and R^2 may together with the nitrogen to which they are attached form a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

wherein suitable optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl, -SO_2Ndi(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms.

In this specification the term "alkoxy" means an alkyl group as defined hereinbefore linked to an oxygen atom.

It is to be understood that optional substituents on any group may be attached to any available atom as appropriate unless otherwise specified, including heteroatoms provided that they are not thereby quaternised.

Within this specification composite terms are used to describe groups comprising more that one functionality such as –(1-6C)alkylNHSO$_2$(1-6C)alkyl. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example –(1-6)alkylNHSO$_2$(1-6C)alkyl includes –methylaminosulphonylmethyl, -methylaminosulphonylethyl, -ethylaminosulphonylmethyl, and -propylaminosulphonylbutyl.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from "0, 1 or 2" groups, "0 or 1" groups and "1 or 2" groups.

Substituents may be present at any suitable position on, for example, an alkyl group. Therefore, hydroxy substituted (1-6C)alkyl includes hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl and isopropyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl, iso-pentyl, 1-2-dimethylpropyl and hexyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(3-8C)cycloalkenyl** include cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl; examples of **(5-12C)bicycloalkyl** include

norbornyl, decalinyl (bicyclo[4,4,0]decyl (cis and trans), bicyclo[5,3,0]decyl and hydrindanyl (bicyclo[4,3,0]nonyl); examples of **(6-12)tricycloalkyl** include adamantyl (tricyclo[3,3,1,1]decyl), homoadamantyl (tricyclo[4,3,1,1]undecyl) and isomers of perhydrophenanthrene; examples of **–(1-6C)alkyl(3-8C)cycloalkyl** include –(1-4C)alkyl(3-6C)cycloalkyl, such as cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylpropyl and cyclohexylbutyl; examples of **–(1-6C)alkyl(3-8C)cycloalkenyl** include –(1-4C)alkyl(3-6C)cycloalkenyl, such as cyclopropenylmethyl, cyclopropenylethyl, cyclopropenylpropyl, cyclopropenylbutyl, cyclobutenylmethyl, cyclopentenylethyl, cyclohexenylmethyl and cyclohexadienylmethyl; examples of **(1-6C)alkoxy** include methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy and pentoxy; examples of **halo** are chloro, bromo, fluoro and iodo; examples of **halo(1-6C)alkyl** include fluoroethyl and fluoromethyl; examples of **dihalo(1-6C)alkyl** include difluoromethyl, 1,2-difluoroethyl and 1,1-difluoroethyl; examples of **hydroxy(1-6C)alkyl** include hydroxy methyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxybutyl; examples of **carboxy(1-6C)alkyl** include carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 2-carboxypropyl and 3-carboxypropyl; examples of **carboxy(1-6C)alkoxy** include carboxymethoxy, 1-carboxyethoxy, 2-carboxyethoxy, 2-carboxypropoxy and 3-carboxypropoxyl; examples of **(1-6C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-6C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and di-isopropylamino; examples of **–CO(1-6C)alkyl** include –CO(1-4C)alkyl such as methylcarbonyl, ethylcarbonyl, propylcarbonyl, iso-propylcarbonyl and tert-butylcarbonyl; examples of **–CO_2(1-6C)alkyl** include –CO_2(1-4C)alkyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl and tert-butoxycarbonyl; examples of **–NHCO(1-6C)alkyl** include –NHCO(1-4C)alkyl such as methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, iso-propylcarbonylamino and tert-butylcarbonylamino; examples of **–CONH(1-6C)alkyl** include –CONH(1-4C)alkyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, iso-propylaminocarbonyl and tert-butylaminocarbonyl; examples of **–CONdi(1-6C)alkyl** include –CONdi(1-4C)alkyl such as dimethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, diethylaminocarbonyl, N-methyl-N-propylaminocarbonyl and di-isopropylaminocarbonyl; examples of **–SO_2NH(1-6C)alkyl** include –SO_2NH(1-4C)alkyl such as methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, iso-propylaminosulfonyl and tert-butylaminosulfonyl; examples of **–SO_2Ndi(1-6C)alkyl** include –SO_2Ndi(1-4C)alkyl

such as dimethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl, diethylaminosulfonyl, N-methyl-N-propylaminosulfonyl and di-isopropylaminosulfonyl; examples of **–NHSO$_2$(1-6C)alkyl** include –NHSO$_2$(1-4C)alkyl such as methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, iso-propylsulfonylamino and tert-butylsulfonylamino;

examples of **–(1-6C)alkylCO(1-6C)alkyl** include –(1-4C)alkylCO(1-4C)alkyl such as methylcarbonylmethyl, methylcarbonylbutyl, ethylcarbonymethyl, propylcarbonylbutyl, iso-propylcarbonylmethyl and tert-butylcarbonylmethyl; examples of **–(1-6C)alkylCO(3-8C)cycloalkyl** include –(1-4C)alkylCO(3-6C)cycloalkyl such as cyclopropylcarbonylmethyl, cyclopropylcarbonylbutyl, cyclobutylcarbonymethyl, cyclopentylcarbonylbutyl, cyclohexylcarbonylmethyl and cyclohexylcarbonylmethyl; examples of **–(1-6C)alkylOCO(1-6C)alkyl** include –(1-4C)alkylOCO(1-4C)alkyl such as methylcarbonyloxymethyl, methylcarbonyloxybutyl, ethylcarbonyloxymethyl, propylcarbonyloxybutyl, iso-propylcarbonyloxymethyl and tert-butylcarbonyloxymethyl; examples of **–(1-6C)alkylOCO(3-8C)cycloalkyl** include –(1-4C)alkylOCO(3-6C)alkyl such as cyclopropylcarbonyloxymethyl, cyclopropylcarbonyloxybutyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxybutyl, cyclohexylcarbonyloxymethyl and cyclohexylcarbonyloxymethyl; examples of **–(1-6C)alkylCO$_2$(1-6C)alkyl** include –(1-4C)alkylCO$_2$(1-4C)alkyl such as methoxycarbonylmethyl, methyoxycarbonylbutyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, iso-propoxycarbonylmethyl and tert-butoxycarbonylmethyl; examples of **–(1-6C)alkylCO$_2$(3-8C)cycloalkyl** include –(1-4C)alkylCO$_2$(3-6C)cycloalkyl such as cyclopropyloxycarbonylmethyl, cyclopropyloxycarbonylbutyl, cyclobutyloxycarbonylmethyl, cyclopentyloxycarbonylmethyl, cyclohexyloxycarbonylmethyl and cyclohexy;oxycarbonylmethyl; examples of **–(1-6C)alkylNHCO(1-6C)alkyl** include –(1-4C)alkylNHCO(1-4C)alkyl such as methylcarbonylaminomethyl, methylcarbonylaminopropyl, ethylcarbonylaminomethyl, propylcarbonylaminomethyl, iso-propylcarbonylaminomethyl and tert-butylcarbonylaminomethyl; examples of **–(1-6C)alkylNHCO(3-8C)cycloalkyl** include –(1-4C)alkylNHCO(3-6C)cycloalkyl such as cyclopropylcarbonylaminomethyl, cyclopropylcarbonylaminopropyl, cyclobutylcarbonylaminomethyl, cyclopentylcarbonylaminomethyl, cyclohexylcarbonylaminomethyl and cyclohexylcarbonylaminoethyl; examples of **–(1-6C)alkylCONH(1-6C)alkyl** include –(1-4C)alkylCONH(1-4C)alkyl such as methylaminocarbonylmethyl, methylaminocarbonylpropyl, ethylaminocarbonylmethyl, propylaminocarbonylmethyl, iso-

propylaminocarbonylmethyl and tert-butylaminocarbonylmethyl; examples of **–(1-6C)alkylCONdi(1-6C)alkyl** include –(1-4C)alkylCONdi(1-4C)alkyl such as dimethylaminocarbonylmethyl, dimethylaminocarbonylpropyl, N-methyl-N-ethylaminocarbonylmethyl, diethylaminocarbonylmethyl, N-methyl-N-propylaminocarbonylmethyl and di-isopropylaminocarbonylmethyl; examples of **–(1-6C)alkylCONH(3-8C)cycloalkyl** include –(1-4C)alkylCONH(3-6C)cycloalkyl such as cyclopropylaminocarbonylmethyl, cyclopropylaminocarbonylpropyl, cyclobutylaminocarbonylmethyl, cyclopentylaminocarbonylmethyl, cyclohexylaminocarbonylmethyl and cyclohexylaminocarbonylethyl; examples of **–(1-6C)alkylNH(1-6C)alkyl** include –(1-4C)alkylNH(1-4C)alkyl such as methylaminomethyl, methylaminopropyl, ethylaminomethyl, propylaminomethyl, iso-propylaminomethyl and tert-butylaminomethyl; examples of **–(1-6C)alkylNdi(1-6C)alkyl** include –(1-4C)alkylNdi(1-4C)alkyl such as dimethylaminomethyl, dimethylaminopropyl, N-methyl-N-ethylaminomethyl, diethylaminomethyl, N-methyl-N-propylaminomethyl and di-isopropylaminomethyl; examples of **–(1-6C)alkylSO$_2$NH(1-6C)alkyl** include –(1-4C)alkylSO$_2$NH(1-4C)alkyl such as methylaminosulfonylmethyl, methylaminosulfonylpropyl, ethylaminosulfonylmethyl, propylaminosulfonylmethyl, iso-propylaminosulfonylmethyl and tert-butylaminosulfonylmethyl; examples of **–(1-6C)alkylSO$_2$Ndi(1-6C)alkyl** include –(1-4C)alkylSO$_2$Ndi(1-4C)alkyl such as dimethylaminosulfonylmethyl, dimethylaminosulfonylpropyl, N-methyl-N-ethylaminosulfonylmethyl, diethylaminosulfonylmethyl, N-methyl-N-propylaminosulfonylmethyl and di-isopropylaminosulfonylmethyl; examples of **–(1-6C)alkylNHSO$_2$(1-6C)alkyl** include –(1-4C)alkylNHSO$_2$(1-4C)alkyl such as methylsulfonylaminomethyl, methylsulfonylaminopropyl, ethylsulfonylaminomethyl, propylsulfonylaminomethyl, iso-propylsulfonylaminomethyl and tert-butylsulfonylaminomethyl; examples of **–(1-6C)alkylSO$_2$(1-6C)alkyl** include –(1-4C)alkylSO$_2$(1-4C)alkyl such as methylsulfonylmethyl, methylsulfonylpropyl, ethylsulfonylmethyl, propylsulfonylmethyl, iso-propylsulfonylmethyl and tert-butylsulfonylmethyl; examples of **-SO$_2$(1-6C)alkyl** include SO$_2$(1-4C)alkyl such as methylsulfonylethylsulfonyl, propyl, iso-propylsulfonyl and tert-butylsulfonyl.

Examples of **–(1-6C)alkylAR1** include (each example being optionally substituted) benzyl, phenylethyl and phenylbutyl. Examples of **–(1-6C)alkylCOAR1** include (each example being optionally substituted) phenylcarbonylmethyl, phenylcarbonylethyl,

phenylcarbonylpropyl and phenylcarbonylbutyl. Examples of **–(1-6C)alkylCO$_2$AR1** include (each example being optionally substituted) phenoxycarbonylmethyl, phenoxycarbonylethyl, phenoxycarbonylpropyl and phenoxycarbonylbutyl. Examples of **–(1-6C)alkylOCOAR1** include (each example being optionally substituted) phenylcarbonyloxymethyl, phenylcarbonyloxyethyl, phenylcarbonyloxypropyl and phenylcarbonyloxybutyl. Examples of **–(1-6C)alkylNHCOAR1** include (each example being optionally substituted) phenylcarbonylaminomethyl, phenylcarbonylaminoethyl, phenylcarbonylaminopropyl and phenylcarbonylaminobutyl. Examples of **–(1-6C)alkylCONHAR1** include (each example being optionally substituted) phenylaminocarbonylmethyl, phenylaminocarbonylethyl, phenylaminocarbonylpropyl and phenylaminocarbonylbutyl. Examples of **–(1-6C)alkylNHAR1** include (each example being optionally substituted) phenylaminomethyl, phenylaminoethyl, phenylaminopropyl and phenylaminobutyl.

Particular values for **AR2** include, for example, naphthyl, indanyl, indenyl, dihydronaphthyl and 1,2,3,4-tetrahydronaphthyl.

Examples of **–(1-6C)alkylAR2** include (each example being optionally substituted) naphthylmethyl, naphthylethyl, indanylmethyl, indanylethyl, indanylpropyl, indanylbutyl, indenylmethyl, indenylethyl, dihydronaphthylmethyl, dihydronaphthylpropyl and 1,2,3,4-tetrahydronaphthylmethyl.

Particular values for **HET1** include, for example (each example being optionally substituted) furyl, pyrrolyl, thiophenyl (thienyl), pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-trazinyl, 1,3,5-trazinyl, 1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, 2-oxopyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl, piperidyl, 2-oxopiperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Further particular values for HET1 include (each value being optionally substituted) furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, piperazinyl and imidazolyl.

Further particular values for HET1 include (each value being optionally substituted)

dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Further particular values for HET1 include (each value being optionally substituted) furyl, thiophenyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrahydrofuranyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, 2-oxopyrrolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidyl and 2-oxopiperidyl.

Further particular values for HET1 include (each value being optionally substituted) furyl, thiophenyl, pyridyl, thiazolyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, 2-oxopyrrolidinyl, morpholinyl, thiomorpholinyl, and piperidyl.

Further particular values for HET1 include (each value being optionally substituted) furyl, thiophenyl, pyridyl, thiazolyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, 2-oxopyrrolidinyl, morpholinyl and piperidyl.

It will be appreciated that, when R^1 and R^2 together with the nitrogen to which they are attached form a ring HET1, the ring HET1 must be one which allows the ring to be linked through a nitrogen atom to the carbonyl group to which it is attached and which when linked the nitrogen atom is not quaternised. Suitable values within the particular values for HET1 set out herein include, for example, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, dihydropyrrolyl, tetrahydropyrrolyl, pyrrolidinyl, 2-oxopyrrolidinyl, oxazolidinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidyl or 2-oxopiperidyl.

Examples of **–(1-6C)alkylHET1** include any one of the above particular values for HET1 attached to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylmethyl, pyridylethyl, pyridylpropyl, pyridylbutyl and pyridylhexyl.

Examples of **–(1-6C)alkylCOHET1** include any one of the above particular values for HET1 attached through a carbonyl group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylcarbonylmethyl, pyridylcarbonylethyl, pyridylcarbonylpropyl, pyridylcarbonylbutyl and pyridylcarbonylhexyl.

Examples of **–(1-6C)alkylCO$_2$HET1** include any one of the above particular values for HET1 attached through an oxycarbonyl group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridyloxycarbonylmethyl, pyridyloxycarbonylethyl, pyridyloxycarbonylpropyl, pyridyloxycarbonylbutyl and

pyridyloxycarbonylhexyl.

Examples of **-(1-6C)alkylOCOHET1** include any one of the above particular values for HET1 attached through an carboxy group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylcarboxymethyl, pyridylcarboxyethyl, pyridylcarboxypropyl, pyridylcarboxybutyl and pyridylcarboxyhexyl.

Examples of **-(1-6C)alkylNH(HET1)** include any one of the above particular values for HET1 attached through an amino group to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) pyridylaminomethyl, pyridylaminoethyl, pyridylaminopropyl, pyridylaminobutyl and pyridylaminohexyl.

Particular values for **HET2** include for example indole, benzofuranyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl, indolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydrobenzofuranyl, chromanyl, isochromanyl, 2,3-dihydrobenzthiazolyl, 2,3-dihydrobenzimidazolyl, benzodioxolanyl, purinyl and naphthyridinyl.

Further particular values for **HET2** include for example, indole, benzofuranyl, benzothiophenyl, quinolinyl and isoquinolinyl.

Further particular examples of **HET2** include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 3H-pyrrolo[1,2-a]pyrrolyl, pyrrolo[2,1-b]thiazolyl, 1H-imidazo[1,2-a]pyrrolyl, 1H-imidazo[1,2-a]imidazolyl, 1H,3H-pyrrolo[1,2-c]oxazolyl, 1H-imidazo[1,5-a]pyrrolyl, pyrrolo[1,2-b]isoxazolyl, imidazo[5,1-b]thiazolyl, imidazo[2,1-b]thiazolyl, indolizinyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, pyrazolo[1,5-a]pyridyl, pyrrolo[1,2-b]pyridazinyl, pyrrolo[1,2-c]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-a]pyrimidinyl, pyrido[2,1-c]-s-triazolyl, s-triazole[1,5-a]pyridyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-a]pyrimidinyl, imidazo[1,2-b]-pyridazinyl, s-triazolo[4,3-a]pyrimidinyl, imidazo[5,1-b]oxazolyl and imidazo[2,1-b]oxazolyl. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazinyl, [3H]-oxazolo[3,4-a]pyridyl, [6H]-pyrrolo[2,1-c]oxazinyl and pyrido[2,1-c][1,4]oxazinyl. Other specific examples of 5/5- bicyclic ring systems are imidazooxazolyl or imidazothiazolyl, in particular imidazo[5,1-b]thiazolyl, imidazo[2,1-b]thiazolyl,

imidazo[5,1-b]oxazolyl or imidazo[2,1-b]oxazolyl.

Examples of **–(1-6C)alkylHET2** include any one of the above particular values for HET2 attached to any value of (1-6C)alkyl, and thus includes for example (optionally substituted) indolylmethyl, indolylethyl, indolylpropyl, indolylbutyl and indoylhexyl.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen)", W.L.Mosby (Interscience Publishers Inc., New York), 1961, Parts 1 and 2.

Particuler values for **HET3** include, for example, indolyl, benzimidazolyl, indolinyl, 1,2,3,4-tetrahydroquinolyl, 2,3-dihydrothiazolyl, 2,3-dihydrobenzimidazolyl and purinyl.

Particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl, $-SO_2N$di(1-6C)alkyl, $–NHSO_2$(1-6C)alkyl, -CO(1-6C)alkyl, $-CO_2$(1-6C)alkyl and –OCO(1-6C)alkyl.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1, 2 or 3, substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl, $–NHSO_2$(1-6C)alkyl.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1 or 2 substituents independently selected from cyano, halo, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, amino, methylamino, ethylamino, $-CONH_2$, –CONHMe, –NHCOMe, $-S(O)_2NH_2$, $–SO_2NHMe$ and $–NHSO_2Me$.

Further particular values for optional substituents on AR1, AR2, HET1 and HET2 are 1 or 2 substituents independently selected from cyano, fluoro, chloro, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, $-CONH_2$ and $-S(O)_2NH_2$.

If not stated elsewhere, suitable optional substituents for a particular group are those as stated for similar groups herein.

A compound of formula (I) may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable

salts may be made by conventional methods such as those described following.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DPP-IV activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It will be appreciated by those skilled in the art that certain compounds of formula (I) contain asymmetrically substituted carbon and/or sulphur atoms, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DPP-IV activity, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DPP-IV activity by the standard tests described hereinafter. Generally compounds having the (R)-configuration at the carbon atom bearing R^3 and R^4 are preferred.

It is also to be understood that certain compounds of the formula (I) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to

be understood that the invention encompasses all such solvated forms which inhibit DPP-IV activity.

As stated before, we have discovered a range of compounds that have good DPP-IV inhibitory activity. They have good physical and/or pharmacokinetic properties in general. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

Particular aspects of the invention comprise a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein the substituents Ar, R^1 to R^9 and other substituents mentioned above have values defined hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I).

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

1) Ar is unsubstituted phenyl

2) Ar is phenyl substituted with 1 group R^9

3) Ar is phenyl substituted with 2 groups independently selected from R^9

4) Ar is phenyl substituted with 4 groups independently selected from R^9

5) R^9 is halo, preferably fluoro

6) R^9 is (1-6C)alkyl (optionally substituted with 1-5 halo), for example (1-4C)alkyl (optionally substituted with 1-5 halo), such as methyl, fluoromethyl, difluoromethyl or trifluoromethyl

7) R^9 is (1-6C)alkoxy (optionally substituted with 1-5 halo), for example (1-4C)alkoxy (optionally substituted with 1-5 halo), such as methoxy, fluoromethoxy, difluoromethxoy or trifluoromethoxy

8) R^9 is cyano

9) R^1 is hydrogen

10) R^1 is (1-6C)alkyl, for example (1-4C)alkyl, such as methyl

11) R^5 is hydrogen or methyl

12) R^5 is hydrogen

13) R^6 is hydrogen or methyl

14) R^6 is hydrogen

15) R^7 is hydrogen or methyl

16) R^7 is hydrogen

17) R^8 is hydrogen or methyl

18) R^8 is hydrogen

19) R^3 and R^4 together form a ring as defined by AR2, HET1 or HET2

20) R^3 and R^4 together form a ring as defined by AR2

21) R^3 and R^4 together form a ring as defined by HET1

22) R^3 and R^4 together form a ring as defined by HET2

23) R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

24) R^3 is hydrogen and R^4 is -(1-6C)alkylAR1 such as benzyl

25) R^3 is hydrogen and R^4 is -(1-6C)alkylAR2

26) R^3 is hydrogen and R^4 is -(1-6C)alkylHET1

27) R^3 is hydrogen and R^4 is -(1-6C)alkylHET2

28) R^3 is (1-6C)alkyl, such as (1-4C)alkyl, for example methyl and R^4 is selected from -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

29) R^3 is hydrogen and R^4 is selected from -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

30) R^1 is hydrogen and R^2 is a (3-8C)cycloalkyl, (5-12C)bicycloalkyl, (6-12C)tricycloalkyl ring or a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1

31) R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, and (6-12C)tricycloalkyl

32) R^2 is selected from AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1 and -(1-6C)alkylHET2

33) R^2 is selected from -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1 and -(1-6C)alkylOCOHET1

34) R^2 is selected from -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1 and -(1-6C)alkylCOHET1

35) R^2 is selected from -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl and -(1-6C)alkylCONHAR1

36) R^2 is selected from -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl, -(1-6C)alkylNHAR1 and -(1-6C)alkylNH(HET1)

37) R^2 is selected from -(1-6C)alkylNHSO_2(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl and -(1-6C)alkylSO_2N-di(1-6C)alkyl

38) R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO_2(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl and -(1-6C)alkylSO_2N-di(1-6C)alkyl

39) R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO_2(1-6C)alkyl and -(1-6C)alkylSO_2NH(1-6C)alkyl

40) R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), and -(1-4C)alkylNHSO_2(1-4C)alkyl

41) R^1 and R^2 together with the nitrogen to which they are attached form a ring defined by

HET1, optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1

42) R^1 and R^2 together with the nitrogen to which they are attached form a ring defined by HET3

43) R^1 is H and R^2 is a furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,3- & 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxazinyl, oxadiazolyl, thiazolyl, isothiazolyl, 1,2,4- and 1,3,4-thiadiazolyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl, piperidyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl or 1,4-dioxan-2-yl ring, optionally substituted as hereinbefore described

44) R^1 is H and and R^2 is a furyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, oxazoline, thiazoline, dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl, imidazolyl or piperidyl ring optionally substituted as hereinbefore described

45) R^1 and R^2 together with the nitrogen to which they are attached form a dihydropyrrolyl (especially 2,5-dihydropyrrol-4-yl), tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, , tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl

46) R^1 and R^2 together with the nitrogen to which they are attached form a tetrahydropyridyl (especially 1,2,5,6-tetrahydropyrid-4-yl), tetrahydrofuranyl, pyrrolidinyl, oxazolidine, thiazolidine, morpholinyl, thiomorpholinyl, piperazinyl or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-

6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl

47) R^1 and R^2 together with the nitrogen to which they are attached form a pyrrolidinyl, or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-4C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, -$CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, -$S(O)_2NH_2$, –SO_2NH(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl

48) R^1 and R^2 together with the nitrogen to which they are attached form a pyrrolidinyl, or piperidyl ring optionally substituted by 1 or 2 substituents independently selected from cyano, halo, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, amino, methylamino, ethylamino, -$CONH_2$, –CONHMe, –NHCOMe, -$S(O)_2NH_2$, –SO_2NHMe and –$NHSO_2$Me

49) R^1 is hydrogen

50) R^1 is methyl

51) Ar is phenyl substituted with 3 groups independently selected from R^9, and particularly three fluoro groups

52) Ar is 2-fluorophenyl

53) Ar is 2,4-difluorophenyl

54) Ar is 2,5-difluorophenyl

55) R^2 is (1-4C)alkyl, for example methyl

56) R^2 is hydrogen, (1-6C)alkyl, (1-6C)alkylSO_2(1-6C)alkyl, (1-6C)alkylCONH(1-6C)alkyl, -SO_2(1-6C)alkyl, (1-6C)alkyl(3-8C)cycloalkyl, (1-6C)alkyl$NHSO_2$(1-6C)alkyl, (1-6C)alkylCONHAR1 or (1-6C)alkylHET1

Further particular groups of compounds of the invention within any of the groups of compounds defined herein are those in which R^3 is hydrogen or (1-6C)alkyl and R^4 is a group other than hydrogen or (1-6C)alkyl, and wherein the carbon atom bearing R^3 and R^4 has the (R)-configuration.

Further particular groups of compounds of the invention within any of the groups of compounds defined herein are those containing a group HET1 in which HET1 contains a single heteroatom.

In one aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form a ring as defined by AR2, HET1 or HET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form a ring as defined by AR2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1,

-(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form an indanyl ring;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl, fluorophenyl or difluorophenyl;

R^1 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form an indanyl ring;

R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO$_2$NH$_2$ and -SO$_2$NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from

fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, $-SO_2NH_2$ and $-SO_2NHMe$), and -(1-4C)alkylNHSO$_2$(1-4C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from -(1-4C)alkyl(3-8C)cycloalkyl, -(1-4C)alkyl(3-8C)cycloalkenyl, -(1-4C)alkylAR1, -(1-4C)alkylAR2, -(1-4C)alkylHET1 and -(1-4C)alkylHET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from -(1-4C)alkylAR1, -(1-4C)alkylAR2, -(1-4C)alkylHET1 and -(1-4C)alkylHET2;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl,

-(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from benzyl, (optionally substituted with 1 or 2 substituents selected from cyano, fluoro, chloro, methyl, ethyl, fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, methoxy, carboxymethyl, carboxymethoxy, hydroxy, -CONH$_2$ and -S(O)$_2$NH$_2$;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl, fluorophenyl or difluorophenyl;

R^1 is hydrogen;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen;

R^4 is benzyl;

R^2 is selected from (1-6C)alkyl, cyclohexyl, norbonyl, adamantyl, phenyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), benzyl (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONHPh (optionally substituted by 1 or 2 substituents selected from fluoro, chloro, trifluoromethyl, methanesulfonamido, carboxymethyl, -SO_2NH_2 and -SO_2NHMe), and -(1-4C)alkylNHSO$_2$(1-4C)alkyl.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl substituted with 1, 2 or 3 fluoro;

R^1 is hydrogen;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1 and -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl;

R^3 is hydrogen;

R^4 is CH_2-AR1, CH_2-HET1 or CH_2-HET2; and

R^5, R^6, R^7 and R^8 are all hydrogen.

In another aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl substituted with 1, 2 or 3 fluoro;

R^1 is hydrogen;

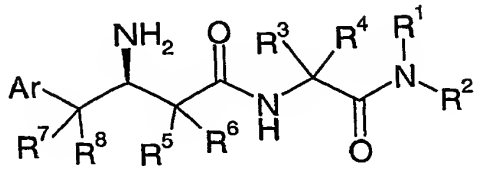
R^2 is hydrogen, (1-4C)alkyl, -(1-4C)alkylAR1 or -(1-4C)alkylCONH(1-4C)alkyl;

R^3 is hydrogen;

R^4 is CH_2-AR1 or CH2-HET1; and

R^5, R^6, R^7 and R^8 are all hydrogen.

Particular compounds of the invention are of the formula (IA):



(IA)

wherein Ar, R^1 to R^8 are as defined in any one of the definitions, embodiments or aspects contained herein before or hereinafter.

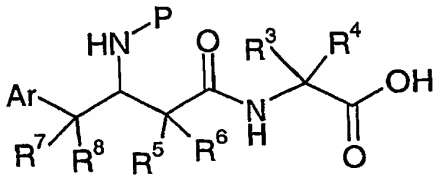
In another aspect of the invention, compounds of the invention are any one of the Examples, or a pharmaceutically acceptable salt thereof.

Process

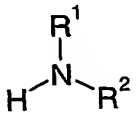
A compound of formula (I) and its pharmaceutically-acceptable salts may be prepared by any process known to be applicable to the preparation of chemically related compounds. Such processes, when used to prepare a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention.

In a further aspect the present invention also provides that the compounds of the formulae (I) and pharmaceutically-acceptable salts thereof, can be prepared by a process comprising the following steps (wherein the variables are as defined hereinbefore or after unless otherwise stated) :

a) coupling of a compound of formula (II) (or an activated derivative thereof) (wherein P is a suitable protecting groups) with a compound of formula (III), followed by removal of the protecting group P;

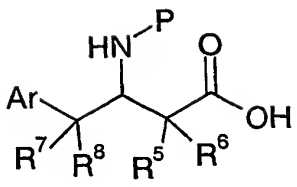


(II)

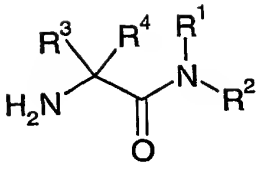


(III)

or b) coupling of a compound of formula (IV) (or an activated derivative thereof) with a compound of formula (V) followed by removal of the protecting group P;



(IV)



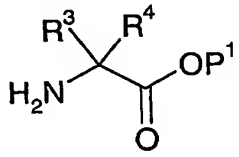
(V)

and thereafter if desirable or necessary

(i) converting a compound of formula (I) into another compound of formula (I) using conventional functional group modification; and/or

(ii) optionally forming a pharmaceutically acceptable salt.

Compounds of the formula (II) are commercially available or may be made by processes known in the art. For example, compounds of the formula (II) may be made by coupling a compound of formula (IV) (or an activated derivative thereof) with a compound of formula (V), wherein P^1 is a suitable protecting group;



(V)

followed by removal of P^1 under suitable conditions.

Compounds of the formula (IV) are generally commercially available or may be made by processes known in the art for making β-amino acids. Suitably the protecting group P is a carbamate protecting group such as a BOC group. Further processes for making β-amino acids are found in patent application WO 03/000181.

Compounds of the formula (V) are generally commercially available or may be made by processes known in the art for making protected forms of amino acids. Suitably the protecting group P^1 is an alkyl group, such as methyl.

Suitable coupling conditions for step b) or step c) are any of those known in the art for coupling together acids and bases for example standard peptide coupling reagents known in the art, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable

solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C. Reference to an "activated derivative" of a compound of formula (II) or (IV) means for example, a derivative such as an anhydride or acid halide suitable for such coupling reactions.

Removal of the proptecting group P^1 may be achieved by any suitable method known in the art. Where P^1 is an alkyl group, the ester may be hydrolysed under acid or basic conditions, for example using alkali bases such as sodium hydroxide or lithium hydroxide.

Removal of the proptecting group P may be achieved by any suitable method known in the art. Where P is a carbamate group such as a BOC group, hydrolysis of the BOC group may be achieved using aqueous acid, for example a solution of aqueous HCl in dioxane. Conditions suitable for removing the protecting group P, such as treatment with an acid such as HCl, may result in formation of a salt of a compound of the formula (I), which may optionally be treated to give the free base form or to give an alternative (pharmaceutically acceptable) salt form.

If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, techniques which are described or illustrated in the references given above, or techniques which are analogous to the above described procedure or the procedures described in the examples.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will be appreciated that some intermediates to compounds of the formula (I) are also novel and these are provided as separate independent aspects of the invention. Certain compounds of formula (II) are novel and are provided as a further independent aspect of the invention. Certain compounds of formula (III) are novel and are provided as a further independent aspect of the invention. Certain compounds of formula (IV) are novel and are

provided as a further independent aspect of the invention. Certain compounds of formula (V) are novel and are provided as a further independent aspect of the invention.

Particular compounds of formula (II), (III), (IV) and (V) are those wherein Ar is phenyl substituted with 1, 2 or 3 fluoro; R^5, R^6, R^7 and R^8 are all hydrogen; R^3 is hydrogen and R^4 is CH_2-AR1, CH_2-Het1 or CH_2-Het2, R^1 is hydrogen and R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products.

The removal of any protecting groups and the formation of a pharmaceutically-acceptable salt are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps has been provided hereinbefore.

When an optically active form of a compound of the invention is required, it may be

obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. In one aspect, the composition of the inventions is in a form suitable for oral use.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the

gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary

from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

According to a further aspect of the present invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit DPP-IV activity and are therefore of interest for their blood glucose-lowering effects.

A further feature of the present invention is a compound of formula (I) and pharmaceutically-acceptable salts thereof for use as a medicament.

Conveniently this is a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use as a medicament for producing an inhibition of DPP-IV activity in a warm-blooded animal such as a human being.

Particularly this is a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use as a medicament for treating diabetes mellitus in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the production of an inhibition of DPP-IV activity in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the treatment of diabetes mellitus in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in producing an inhibition of DPP-IV activity in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) as defined hereinbefore or a

pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier for use in the treatment of diabetes mellitus in an warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided a method for producing an inhibition of DPP-IV activity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating diabetes mellitus in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As stated above compounds defined in the present invention are of interest for their ability to inhibit the activity of DPP-IV. A compound of the invention may therefore be useful for the prevention, delay or treatment of a range of disease states including diabetes mellitus, more specifically type 2 diabetes mellitus (T2DM) and complications arising there from (for example retinopathy, neuropathy and nephropathy), impaired glucose tolerance (IGT), conditions of impaired fasting glucose, metabolic acidosis, ketosis, dysmetabolic syndrome, arthritis, osteoporosis, obesity and obesity related disorders, peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, muscle weakness, hyperlipidaemias, Alzheimer's disease , atherosclerosis, infertility, polycystic ovary syndrome, various immunomodulatory diseases (such as psoriasis), HIV infection, inflammatory bowel syndrome, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis.

In a further aspect, compounds of the formula (I) or their pharmaceutically acceptable

salts may be administered in combination with other therapeutic agents in order to prevent, delay or treat the various disease states in which DPP-IV activity is implicated, including but not limited to those disease states listed above

For example, in order to prevent, delay or treat type 2 diabetes mellitus, the compounds of the present invention or their pharmaceutically-acceptable salts may be administered in combination with a therapeutically effective amount of one or more other compounds of the formula (I) and/or one or more of the following agent(s):

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas, prandial glucose regulators and glucokinase activators;
3) Agents that improve incretin action (for example GLP-1 agonists);
4) Insulin sensitising agents including PPARgamma agonists and agents with combined PPARalpha and gamma activity;
5) Agents that modulate hepatic glucose balance (for example biguanides, fructose 1, 6 bisphosphatase inhibitors, glycogen phosphorylase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators);
6) Agents designed to reduce the absorption of glucose from the intestine (for example alpha glucosidase inhibitors);
7) Agents that prevent the reabsorption of glucose by the kidney (sodium glucose transporter inhibitors);
8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors, Protein Kinase C inhibitors);
9) Agents used to treat obesity (for example appetite suppressants) or that increase energy expenditure;
10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors, PPAR alpha agonists (for example fibrates), PPAR delta agonists, bile acid sequestrants, cholesterol absorption inhibitors, bile acid absorption inhibitors, CETP inhibitors, inhibitors of lipolysis;
11) Antihypertensive agents such as, beta blockers, ACE inhibitors, Calcium antagonists, Angiotensin receptor antagonists, alpha receptor antagonists and diuretic agents;
12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents, thrombin antagonists, factor Xa inhibitors, factor VIIa inhibitors, antiplatelet agents and anticoagulants;

13) Agents which antagonise the actions of glucagon; and

14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs and steroidal anti-inflammatory agents.

In addition to its use in therapeutic medicine, compounds of formula (I) and their pharmaceutically-acceptable salts are also useful as pharmacological tools in the development and standardisation of in-vitro and in-vivo test systems for the evaluation of the effects of inhibitors of DPP-IV activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

As indicated above, all of the compounds, and their corresponding pharmaceutically-acceptable salts, are useful in inhibiting DPP-IV. The ability of the compounds of formula (I), and their corresponding pharmaceutically-acceptable acid addition salts, to inhibit DPP-IV may be demonstrated employing the caco-2 DPP-IV Assay which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression was accomplished as described by Reisher, et al. (Proc. Natl. Acad. Sci., Vol. 90, pgs. 5757–5761 (1993)). Cell extract is prepared from cells solubilized in 10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u.aprotinin, 0.5% nonidet-P40, pH 8.0, which is centrifuged at 35,000 g for 30 min at 4°C to remove cell debris.

The colorimetric assay is conducted by adding 20 µg solubilized Caco-2 protein, 20 ng of recombinant human DPPIV or purified porcine kidney DPP-IV, in a final volume of 10ul in assay buffer (25 mM Tris HCl pH 7.4, 140mM NaCl, 10 mM KCl,0.1% Triton-x-100) to microtiter plate wells. After a 10 min. incubation at room temperature, the reaction is initiated by adding 10 µl of 0.5 mM substrate (H-Glycine -Proline-pNA; pNA is p-nitroaniline). The final assay volume is 100µl. The reaction is carried out at room temperature for 10 minutes after which time a 10 µl volume of sodium acetate buffer pH 4.5 is added to stop the reaction. Test compounds are typically added as 10 µl additions A standard curve of free p-nitroaniline is generated using 0-500 µM solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The endpoint is determined by measuring absorbance at 405 nm in a Labsystems microtiter plate reader.

Activity of CaCo2 extract is also measured employing a modified version of the assay described in Kubota, et al. (Clin. Exp.Immunol., Vol.89, pgs. 192-197 (1992)). The assay is conducted by adding 10 µg solubilized Caco-2 protein, in a final volume of 10 ul assay buffer (25 mMHEPES, 140 mM NaCI, 80 mM MgCl2, 0.1% Triton X-100, pH 7.4) to micro titer plate wells. After 10 min incubation at room temperature, the reaction is initiated by the addition of 10 µI of incubation buffer containing 0.5 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-40-methylcoumarin). The plates are at room temperature (in the dark) for 10 min. Test compounds are typically added as 10 µI additions and the final assay buffer volume is 100µl. The reaction is initiated by adding 10 µI of 0.5 mM substrate Gly-Pro-7-amino-4-trifluoromethylcoumarin for 10 minutes after which time a 10 µI volume of sodium acetate buffer pH4.5 is added to stop the reaction. After the 10 min. reaction, florescence is measured using a Tecan Ultra fluorimeter (Excitation 360 mn Emission 465 nm). .A standard curve of free AMC is generated using 0-50 µM solutions of free AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 11-point, dose-response curves using a 4 parameter logistic function.

Using this assay the compounds generally show activity with $IC_{50} < 100$ µM. Example 1 showed an $IC_{50} = 0.46$ µM, and Example 10 showed an $IC_{50} = 0.45$ µM.

The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described above. Briefly, 5-10 µI of plasma are added to 96-well flat-bottom microtiter plates instead of CaCo2 extract, final assay volume is 100µl. As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 11-point, dose-response curves using a 4 parameter logistic function.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; where a Biotage cartridge is referred to this means a cartridge containing KP-SIL™ silica, 60Å, particle size 32-63mM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data (^{1}H) is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz (unless otherwise stated) using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent; s = singlet, d= doublet, sept = septet, q = quartet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, brs = broad singlet;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in volume : volume (v/v) terms;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

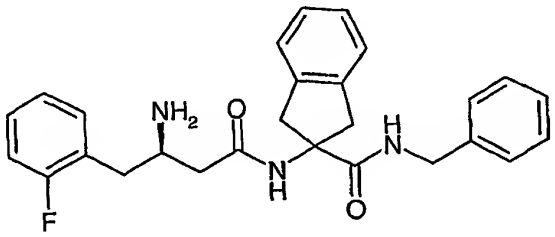
(x) The following abbreviations are used:

Et_2O	ether / diethyl ether
DMF	dimethylformamide;
DCM	dichloromethane
DME	dimethoxyethane;

MeOH	methanol
EtOH	ethanol;
H_2O	water;
TFA	trifluoroacetic acid
THF	tetrahydrofuran
DMSO	dimethylsulfoxide
HOBt	1-hydroxybenzotriazole
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride
DIPEA	diisopropylethylamine
DEAD	diethylazodicarboxylate
BOC	*tert*-butoxycarbonyl

Each of the following Examples is provided as a separate and independent aspect of the invention.

Example 1: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-benzylindane-2-carboxamide hydrogen chloride salt



4M HCl in dioxane was added to *tert*-butyl[(1*R*)-3-(2-[(benzylamino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate (**Intermediate 1,** 104 mg, 0.191 mmol) and the mixture was stirred for 2 hours. The solvent was evaporated under reduced pressure and the residue triturated with ether. The ether was evaporated to afford the title compound as a colourless solid (88 mg, 96%). MS ESP+ m/z 360, 362; ESP- m/z 336, 338. ^{1}H NMR (DMSO): 2.78-2.85 (m, 2H), 2.95-3.02 (m, 2H), 3.10.3.25 (m, 3H), 3.51-3.57 (m, 5H), 4.23-4.27 (m, 2H), 7.05-7.27 (m, 13H), 8.16 (brs 2H), 8.37 (t, 1H), 8.63 (s, 1H); MS m/z 445 $(MH)^+$.

Examples 2-4

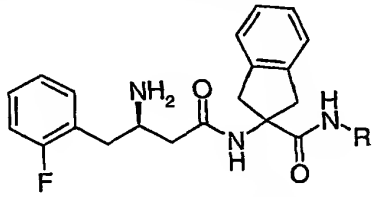
The following examples were made by an analogous method to Example 1. The starting materials were obtained using an analogous procedure to that described below for the

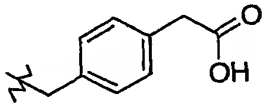
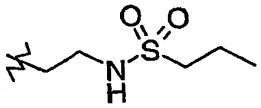
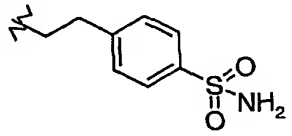
preparation of Intermediate 1, but using the appropriate amine starting materials (commercially available for Examples 3 and 4; for Example 2 see CAS no. [479586-24-8] - reactant in Patent Application WO 2003045382) in place of benzylamine.

Example 2: [4-({[(2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}methyl)phenyl]acetic acid

Example 3: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[(propylsulfonyl)amino]ethyl}indane-2-carboxamide

Example 4: 2-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}indane-2-carboxamide



Example	R	^{1}H NMR (DMSO)	MS m/z
2		2.35-2.41 (m, 2H), 2.70-2.80 (m, 1H), 2.90-2.97 (m, 1H), 3.08-3.23 (m, 2H), 3.35-3.60 (m, 5H), 4.20-4.24 (m,1H), 7.05-7.32 (m, 12H), 7.95 (brs, 2H), 8.30 (t, 1H), 8.57 (s, 1H)	504 $(MH)^+$
3		0.95 (t, 3H), 1.60-1.70 (m, 2H), 2.41-2.43 (m, 2H), 2.77-2.84 (m, 1H), 2.90-2.95 (m, 5H), 3.07-3.17 (m, 4H), 3.38-3.48 (m, 2H), 3.60-3.66 (m, 1H), 6.95 (t, 1H), 7.07-7.17 (m, 6H), 7.22-7.33 (m, 2H), 7.87 (t, 1H), 8.04 (brs, 2H), 8.61 (s, 1H)	505 $(MH)^+$
4		2.39-2.41 (m, 2H), 2.70-2.79 (m, 2H), 2.94-3.10 (m, 2H), 3.25-3.37 (m, 2H), 3.35-3.40 (m, 4H), 3.60-3.62 (m, 1H), 7.06-7.17 (m, 6H), 7.71 (d, 2H), 7.90 (t, 1H), 8.06 (brs, 2H), 8.54 (s, 1H)	538 $(MH)^+$

Intermediate for Example 2

***Tert*-Butyl {4-({[2-{[(3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}methyl)phenyl]acetate**

^{1}H NMR (DMSO): 1.23 (s, 9H), 1.36 (s, 9H) 2.25 (d, 1H), 2.55-2.62 (m, 1H), 2.73-2.77 (m, 1H), 3.12-3.21 (m, 1H), 3.44-3.52 (m, 4H), 3.94-4.03 (m, 1H), 4.11-4.32 (m, 2H), 6.61 (d, 1H), 7.03-7.20 (m, 12H), 8.16 (t, 1H), 8.25 (s, 1H); MS m/z 682 (M+Na).

Intermediate for Example 3

***Tert*-butyl [(*1R*)-1-(2-fluorobenzyl)-3-oxo-3-[({2-[(propylsulfonyl)amino]ethyl}amino) carbonyl]-2,3-dihydro-1*H*-inden-2-yl}aminopropyl]carbamate**

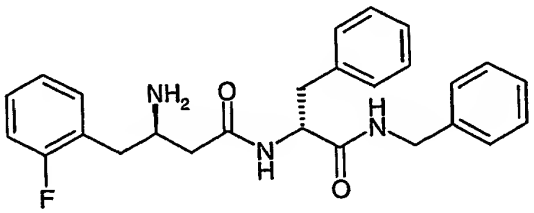
^{1}H NMR ($CDCl_3$): 0.94 (t, 3H), 1.25 (s, 9H), 1.59-1.67 (m, 2H), 2.23 (d, 2H), 2.59-2.62 (m, 1H), 2.72-2.76 (m, 1H), 2.89-2.94 (m, 4H), 3.10-3.14 (m, 4H), 3.41-3.50 (m, 2H), 3.94-3.97 (m, 1H), 6.58 (d, 1H), 6.88 (t, 1H), 7.01-7.21 (m, 8H), 7.71 (brs, 1H), 8.30 (s, 1H); MS m/z 627 (M+Na).

Intermediate for Example 4

***Tert*-butyl [(*1R*)-3-({2-[({2-[4-(aminosulfonyl)phenyl]ethyl}amino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate**

^{1}H NMR ($CDCl_3$): 1.23 (s, 9H), 2.22 (d, 2H), 2.59-2.63 (m, 1H), 2.71-2.76 (m, 3H), 3.03-3.10 (m, 2H), 3.32-3.47 (m, 4H), 3.96-4.00 (m, 1H), 6.61 (d, 1H), 7.04-7.17 (m, 8H), 7.24 (s, 1H), 7.33 (d, 2H), 7.69-7.72 (m, 3H), 8.19 (s, 1H); MS m/z 661 (M+Na).

Example 5: (R)-3-Amino-*N*-((R)-1-benzylcarbamoyl-2-phenyl-ethyl)-4-(2-fluoro-phenyl)-butyramide hydrogen chloride salt.



4M HCl in dioxane was added to (R)-3-Amino-*N*-((R)-1-benzylcarbamoyl-2-phenyl-ethyl)-4-(2-fluoro-phenyl)-butyramide (**Intermediate 4,** 106 mg, 0.191 mmol) and the mixture was stirred for 16 hours. The solvent was evaporated under reduced pressure and the residue triturated with ether. The ether was evaporated to afford the title compound as a colourless solid (90 mg, 96%). ^{1}H NMR (DMSO): 2.20-2.40 (m, 2H), 2.60-2.78 (m, 2H), 2.84 (dd, 1H), 3.00 (dd, 1H), 3.50 (m, 1H), 4.18-4.30 (m, 2H), 4.56 (m, 1H), 7.05-7.38 (m, 14H), 7.94 (brs 2H), 8.44 (d, 1H), 8.58 (t, 1H); MS m/z 434 $(MH)^+$.

Examples 6 to 9

The following examples were synthesised in a similar way to Example 5 using the appropriate commercially available amines in place of benzylamine, but were isolated as the free bases using the following procedure:

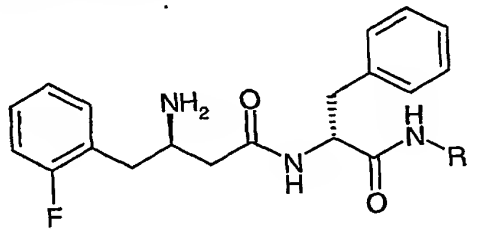
The hydrochloride salt was taken up in DCM (10 ml) and washed sequentially with 2M NaOH (2 x 20 ml) and water (20 ml) the organic layer was dried over $MgSO_4$ and the DCM was removed *in vacuo* to give the free bases as colourless solids.

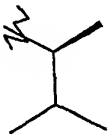
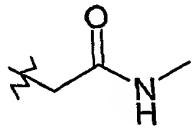
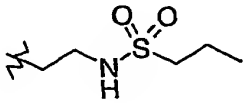
Example 6: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-phenyl-ethyl)-butyramide

Example 7 (R)-3-Amino-*N*-[(R)-1-((S)-1,2-dimethyl-propylcarbamoyl)-2-phenyl-ethyl]-4-(2-fluoro-phenyl)-butyramide

Example 8 (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-1-(methylcarbamoylmethyl-carbamoyl)-2-phenyl-ethyl]-butyramide

Example 9 (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-{(R)-2-phenyl-1-[2-(propane-1-sulfonylamino)-ethylcarbamoyl]-ethyl}-butyramide



Example	R	^{1}H NMR δ:	MS m/z
6		2.19 (dd, 1H), 2.40 (dd, 1H), 2.62-2.82 (m, 5H), 3.0-3.16 (m, 2H), 3.40 (m, 1H), 4.64 ((apparent q, 1H), 6.60 (brs, 1H), 6.96-7.35 (9H, m), 7.64 (brd 1H)	358 $(MH)^+$
7		($CDCl_3$): 0.78 (d, 3H), 0.88 (d, 3H), 1.58 (1H + water), 2.12 (dd, 1H), 2.38 (dd, 1H), 2.62 (dd, 1H), 2.75 (dd, 1H), 3.03 (dd, 1H), 3.11 (dd, 1H), 3.34 (m, 1H), 3.73 (m, 1H), 4.58 (apparent q, 1H), 5.79 (brd, 1H), 6.98-7.32 (m, 9H), 7.77 (d, 1H)	414 $(MH)^+$
8		($CDCl_3$): 2.14 (dd, 1H), 2.39 (dd, 1H), 2.64 (dd, 1H), 2.66-2.80 (m, 4H), 3.02 (dd, 1H), 3.21 (dd, 1H), 3.26 (m, 1H), 3.75 (dd, 1H), 3.86 (dd, 1H), 4.60 (m, 1H), 6.72 (m, 1H), 6.90-7.32 (m, 9H), 7.65 (d, 1H), 7.95 (t, 1H)	415 $(MH)^+$
9		(DMSO): 0.96 (t, 3H), 1.64 (sex, 2H), 2.32 (dd, 1H), 2.40-3.30 (m 11H), 3.49 (m, 1H), 4.42 (m, 1H), 7.02-7.38 (m, 9 H), 8.11 (brs, 3H), 8.20 (t, 1H), 8.32 (d, 1H)	493 $(MH)^+$

Intermediate 1: *Tert*-butyl[(1*R*)-3-(2-[(benzylamino)carbonyl]-2,3-dihydro-1*H*-inden-2-yl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

EDCI (51 mg, 0.27 mmol) followed by HOBt (36 mg, 0.27 mmol) were added to a solution of 2-{[*3R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylic acid (**Intermediate 2,** 0.101 g, 0.22 mmol) in DCM. The mixture was stirred for 2-3 minutes before the addition of triethylamine (30 µl, 0.22 mmol) and benzylamine (20 µl, 0.22 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml) and brine (50 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a colourless solid. The residue was purified by flash silica gel chromatography (ethyl acetate:isohexane 2:3) to give the title compound (104 mg, 86%) as a colourless solid. ^{1}H NMR (DMSO) δ : 1.23 (s, 9H), 2.25 (d, 2H), 2.55-2.62 (m, 1H), 2.70-2.77 (m,1H), 3.13-3.25 (m, 2H), 3.44-3.53 (m, 2H), 3.94-4.04 (m, 1H), 4.16-4.35 (m, 1H), 6.61 (d, 1H), 7.01-7.18 (m, 13H), 8.17 (t, 1H), 8.25 (s, 1H); MS m/z 568 (M+Na).

Intermediate 2: 2-{[3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylic acid

A solution of methyl 2-{[3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylate methyl ester (**Intermediate 3**, 0.292 g, 0.598 mmol) in THF (10 ml) and water (3 ml) was treated with a solution of lithium hydroxide hydrate (50mg 1.19 mmol) in water (1 ml). The reaction mixture was allowed to stir at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure and the aqueous residue was acidified to pH 2 with potassium hydrogen sulfate. The aqueous layer was extracted with ethyl acetate (2 x 100 ml) and the organic phase separated. The combined organics was dried with magnesium sulfate and concentrated under reduced pressure to give the title compound as a colourless solid (0.241 g, 94%). ^{1}H NMR (DMSO): 1.23 (s, 9H), 2.22 (d, 2H), 2.55-2.62 (m, 1H), 2.70-2.82 (m, 2H), 3.11-3.25 (m, 2H), 3.39-3.53 (m, 2H), 3.91-4.01 (brm, 1H), 6.60 (d, 1H), 7.03-7.20 (m, 8H), 8.44 (s, 1H), 12.29 (brs, 1H); MS m/z 455 $(MH)^-$.

Intermediate 3: methyl 2-{[3*R*)-3-[*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl}-indane-2-carboxylate methyl ester

To a stirred solution of (*R*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (0.296 g, 1.0 mmol) in DCM (20 ml) was added sequentially HOBt (0.16 g, 1.2 mmol), EDCI (0.23 g, 1.2 mmol), 2-amino-indan-2-carboxylic acid methyl ester (Kotha, S and Kuki, A *Tetrahedron Lett.*, 1992, **33**, (12) 1565) (0.277 g, 1.0 mmol) and triethylamine (0.28 ml, 2.0 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml), aqueous sodium bicarbonate (50 ml) and brine (100 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a pale yellow gum. The residue was purified by flash silica gel chromatography (ethyl acetate) to give the title compound (325 mg, 69%) as a colourless solid. ^{1}H NMR ($CDCl_3$): 1.35 (s, 9H), 2.26-2.45 (m, 2H), 2.88-2.92 (m, 2H), 3.20-3.29 (m, 2H), 3.62-3.71 (m, 2H), 3.76 (s, 3H), 6.32 (brs, 1H), 6.95-7.02 (m, 2H), 7.14 –7.20 (m, 6H); MS m/z 493 (M+Na).

Intermediate 4: [(R)-2-((R)-1-Benzylcarbamoyl-2-phenyl-ethylcarbamoyl)-1-(2-fluoro-benzyl)-ethyl]-carbamic acid *tert*-butyl ester

To a solution of *N*-[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]-D-phenylalanine (**Intermediate 5**, 0.100g, 0.23 mmol) in DCM (5 mL) was added sequentially HOBt (0.037 g,

0.27 mmol), benzylamine (25 μL, 0.23 mmol), triethylamine (63 μL, 0.45 mmol) and EDCI (0.052 g, 0.27 mmol). The mixture was stirred at ambient temperature for 16 h. and then washed sequentially with 2M HCl (2 X 10 ml), sat. aqueous sodium bicarbonate (10 ml) and water (10 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to give a colourless solid which was purified by flash silica gel chromatography eluting with (DCM to 10 % MeOH/DCM) to give the title compound (0.106 g, 89%) as a colourless solid. ^{1}H NMR (DMSO): 1.22 (s, 9H), 2.18-2.35 (m, 2H), 2.44-2.62 (m, 2H + water), 2.80 (dd, 1H), 3.02 (dd, 1H), 3.92 (m, 1H), 4.06 (d, 2H), 4.60 (m, 1H), 6.57 (d, 1H), 7.00-7.30 (m, 14H), 8.14 (d, 1H), 8.40 (t, 1H)

Intermediate 5: *N*-[(3*R*)-3-*tert*- butoxycarbonylamino-4-(2-fluorophenyl)butanoyl]-D-phenylalanine

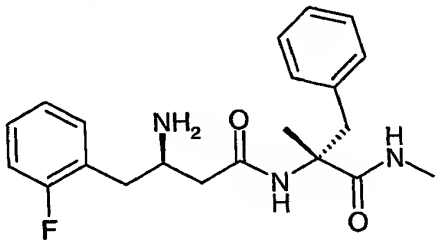
A solution of 2-[(R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyrylamino]-3-phenyl-propionic acid methyl ester (**Intermediate 6,** 2.90 g, 5.88 mmol) in THF (50 mL) and MeOH (3 ml) was treated with a solution of 2M aqueous sodium hydroxide (16.1 mL). The reaction mixture was allowed to stir at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure and the aqueous residue was acidified to pH 2 with 2M HCl at which point a voluminous white precipitate formed, the precipitate was filtered off and washed with water and diethyl ether. The solid was dried *in vacuo* to give the title compound as a colourless solid (0.241 g, 94%). ^{1}H NMR (DMSO): 1.23 (s, 9H), 2.18-2.35 (m, 2H), 2.44-2.62 (m, 2H), 2.87 (dd, 1H), 3.06 (dd, 1H), 3.96 (m, 1H), 4.46 (m, 1H), 6.55 (d, 1H), 7.00-7.30 (m, 9H), 8.22 (d, 1H); MS m/z 467 (M+Na).

Intermediate 6: 2-[(R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyrylamino]-3-phenyl-propionic acid methyl ester

To a stirred solution of (*R*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (2.00 g, 6.75 mmol) in DCM (100 mL) was added sequentially HOBt (1.10 g, 8.11 mmol), methyl D-phenylalaninate (1.46 g, 6.75 mmol), triethylamine (1.88 ml, 13.5 mmol) and EDCI (1.55 g, 8.11 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then washed sequentially with 2M HCl (50 ml), aqueous sodium bicarbonate (50 ml) and brine (100 ml). The organic phase was separated, dried with magnesium sulphate and concentrated under reduced pressure to leave a white gum. The residue was purified by flash silica gel chromatography (eluting with DCM to 10 % MeOH/DCM) to give 2-[(R)-3-*tert*-

Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyrylamino]-3-phenyl-propionic acid methyl ester (2.91 g, 94%) as a colourless solid. ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 2.32 (dd, 1H), 2.42 (dd, 1H), 2.82-2.96 (m, 2H), 3.06 (dd, 1H), 3.14 (dd, 1H), 3.76 (s, 3H), 4.10 (m, 1H), 4.84 (m, 1H), 5.38 (brs, 1H), 6.02 (brd, 1H) and 6.94 –7.36 (m, 9H); MS m/z 481 (M+Na).

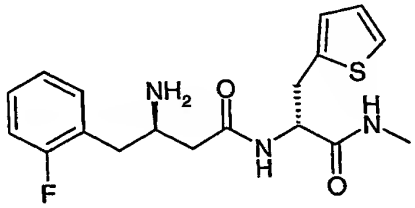
Example 10: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methyl-1-methylcarbamoyl-2-phenyl-ethyl)-butyramide hydrogen chloride salt



To a stirred solution of (R)-2-*tert*-Butoxycarbonylamino-2-methyl-3-phenyl-propionic acid (838mg, 3.0mmol) in DCM (20ml) was added HOBT (500mg, 3.26mmol), EDCI (633mg, 3.3mmol), DIPEA (1.15 ml, 6.6mmol) and methylamine, hydrochloride (223mg, 3.3mmol). The mixture was stirred at RT for 16 hours, evaporated, and the residue was partitioned between ethyl acetate and water. The organic extract was sequentially washed with 1N aqueous citric acid, water, and brine. After drying with magnesium sulphate, the solution was evaporated to give ((R)-1-Methyl-1-methylcarbamoyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester as a white solid (880mg). This material was stirred in 4N HCl/dioxane (10ml) at RT for 2 hours, evaporated and triturated with ether to give (R)-2-Amino-2,*N*-dimethyl-3-phenyl-propionamide, hydrochloride as a white solid (760mg). To a stirred solution of this solid in DCM (20ml) was added (R)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (970 mg, 3.26mmol), HOBT (500mg, 3.26mmol), EDCI (626.4mg, 3.26mmol), DIPEA (1.14 ml, 6.5mmol). The mixture was stirred at RT for 16 hours, evaporated, and the residue was partitioned between ethyl acetate and water. The organic extract was sequentially washed with water, 1N aqueous citric acid, water, 1N aqueous sodium hydroxide, water and brine. After drying with magnesium sulphate, the solution was evaporated to give {(R)-2-(2-Fluoro-phenyl)-1-[((R)-1-methyl-1-methylcarbamoyl-2-phenyl-ethylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester as a white solid. This solid was stirred in 4N HCl/dioxane at RT for 1 hour, evaporated and triturated with ether to give the title compound as a white solid (350mg, 26.4%). ^{1}H NMR (DMSO d_6) δ: 1.18 (s, 3H), 2.52 (d, 3H), 2.85-2.98 (m, 1H), 2.98-

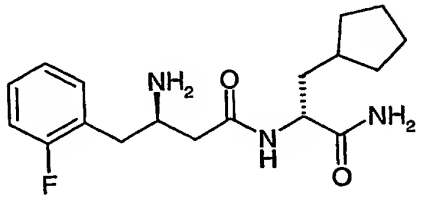
3.1 (m, 2H), 3.28 (s, 2H), 3.58-3.7 (b, 1H), 7.02 (d, 2H), 7.12-7.4 (m, 9H), 7.7 (d, 1H), 7.95 (s, 1H), 8.25 (bs, 3H); MS m/z 372 (MH+).

Example 11: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-thiophen-2-yl-ethyl)-butyramide hydrogen chloride salt



To a stirred solution of (R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid 2,5-dioxo-pyrrolidin-1-yl ester **(Intermediate 8;** 0.515 g, 1.3 mmol) in DCM (20 ml) was added sequentially DIPEA (0.23ml, 1.3 mmol), and (R)-2-amino-*N*-methyl-3-thiophen-2-yl-propionamide hydrochloride **(Intermediate 7**, 0.288 g, 1.3 mmol). The mixture was stirred at ambient temperature for 16 h. The reaction mixture was then filtered and the solid cake was washed with DCM (50 ml) and water (50 ml), then dried under vacuum at 60°C overnight to give {(R)-2-(2-fluoro-phenyl)-1-[((R)-1-methylcarbamoyl-2-thiophen-2-yl-ethylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester (380 mg 63.1%) as a white solid. A solution of this material (195mg, 0.420 mmol) in 4N HCl/dioxane was stirred at room temperature for 1hour. The solvent was removed by evaporation under vacuum and the residue triturated with ether to give the title product (130 mg, 85.3%). ^{1}H NMR (DMSO-d_6) δ: 2.32-2.52 (m, 2H), 2.58 (d, 3H), 2.7-2.82 (m, 1H), 2.88-3.01 (q, 2H), 3.15-3.25 (dd, 1H), 3.59 (b, 1H), 4.38 (b, 1H), 6.79-6.86 (m, 2H), 7.12-7.39 (m, 5H), 8.01 (d, 1H), 8.15 (b, 3H), 8.5 (d, 1H); MS m/z 364 (MH+).

Example 12: (R)-3-Amino-*N*-((R)-1-carbamoyl-2-cyclopentyl-ethyl)-4-(2-fluoro-phenyl)-butyramide hydrogen chloride salt



A solution of **Intermediate 8** (0.394 g, 1.0 mmol), (R)-2-Amino-3-cyclopentyl-propionic acid (0.157mg, 1.0 mmol) and triethylamine (0.139 ml, 1.0 mmol) in dioxane was heated at 150°C for 10 minutes in the microwave oven. After cooling the mixture was partitioned between ethyl acetate (25 ml) and water (25 ml), then the organic phase was washed sequentially with

1M citric acid, water and brine. The organic extract was then dried with magnesium sulphate, and evaporated.. The solid residue was stirred with N–hydroxy succinimide (115mg, 1.0 mmol) and EDCI (192mg, 1.0 mmol) in DCM (20ml) at RT for 16 hours. After evaporation, the residue was partitioned between ethyl acetate and water. The organic phase was washed sequentially with water and brine, dried with magnesium sulphate, filtered and evaporated. The solid residue was stirred with a mixture of dioxane (20 ml) and concentrated aqueous ammonia (5ml) for 16 hours. The resulting precipitate was filtered, washed with water and vacuum dried. The solid obtained was stirred with 4N HCl/dioxane at room temperature for 2 hours.The solution was evaporated and the residue triturated with ether to give the title product as a solid (164mg 48.96%). ^{1}H NMR (DMSO d_6) δ: 0.95-1.18 (b, 2H), 1.37-1.82 (b, 9H), 2.4-2.6 (m, 2H), 2.8-2.9 (dd, 1H), 2.98-3.1 (dd, 1H), 3.62 (b, 1H), 4.13 (b, 1H) 6.92-7.44 (m, 6H), 8.05-8.35 (m, 4H) MS m/z 336 (MH+).

Examples 13-19

The following examples were made as their hydrochloride salts by an analogous method to Example 10; the starting materials are indicated below.

Example 13: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-2-(1*H*-indol-3-yl)-1-methylcarbamoyl-ethyl]-butyramide

Starting material is (R)-2-*tert*-Butoxycarbonylamino-3-(1*H*-indol-3-yl)-propionic acid, commercially available

Example 14: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-butyramide

Starting material (R)-2-*tert*-Butoxycarbonylamino-3-naphthalen-2-yl-propionic acid, commercially available

Example 15: (R)-3-Amino-*N*-[(R)-2-(4-chloro-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide

Starting material (R)-2-*tert*-Butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid, commercially available

Example 16: (R)-3-Amino-*N*-[(R)-2-(4-methyl-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide

Starting material (R)-2-*tert*-Butoxycarbonylamino-3-(4-methyl-phenyl)-propionic acid, commercially available

Example 17: (R)-3-Amino-*N*-[(R)-2-(3,4-difluoro-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide

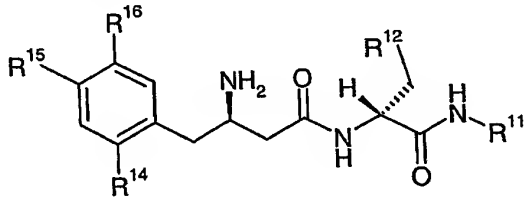
Starting material (R)-2-*tert*-Butoxycarbonylamino-3-(3,4-difluoro-phenyl)-propionic acid, commercially available

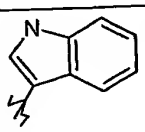
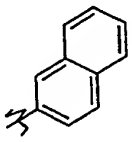
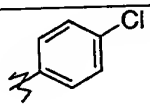
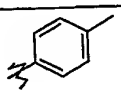
Example 18: (R)-3-Amino-4-(2,4-difluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-phenyl-ethyl)-butyramide

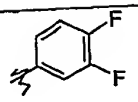
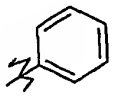
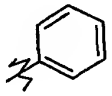
Starting material (R)-2-*tert*-Butoxycarbonylamino-3 -phenyl-propionic acid, commercially available. The starting acid (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2,4-difluorophenyl)butanoic acid was prepared according to the procedure described by R.F.W. Jackson *et al*, *J.Org.Chem.*, 1999, **64**, 7579-7585.

Example 19: (R)-3-Amino-4-(2,5-difluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-phenyl-ethyl)-butyramide

Starting material (R)-2-*tert*-Butoxycarbonylamino-3 -phenyl-propionic acid, commercially available. The starting acid (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid was prepared according to the procedure described by N. Ikemoto *et al*, *J.Amer.Chem.Soc.*, 2004, **126**,(10) 3048-3049.



Example	R^{11}	R^{12}	R^{14}	R^{15}	R^{16}	^{1}H NMR (DMSO) δ:	MS m/z
13	CH_3		F	H	H	2.22-2.45(m, 2H), 2.55(d, 3H), 2.7-3.1(m, 4H), 3.55(b, 1H), 4.42(m, 1H), 6.85-7.35(m, 8H), 7.55(d, 1H), 7.98(d, 1H), 8.1(bs, 3H), 8.4(d, 1H), 10.77(b, 1H)	397
14	CH_3		F	H	H	2.27-2.34 (m, 2H), 2.56 (d, 3H), 2.47-2.89 (m, 2H), 3.10-3.16 (m, 2H), 3.42-3.48 (m, 1H), 4.48-4.55 (m, 1H), 7.06-7.13 (m, 3H), 7.32-7.41 (m, 3H), 7.65 (s, 1H), 7.70-7.76 (m, 3H), 8.02 (d, 2H), 8.51 (d, 1H).	408
15	CH_3		F	H	H	2.27-2.34 (m, 1H), 2.41-2.43 (m, 1H), 2.55 (d, 3H), 2.59-2.70 (m, 2H), 2.82-2.97 (m, 2H), 3.47-3.49 (m, 1H), 4.36-4.44 (m, 1H), 7.11-7.25 (m, 8H), 7.28-7.35 (m, 1H), 7.99-8.04 (m, 2H), 8.45 (d, 1H).	392
16	CH_3		F	H	H	2.09 (s, 3H), 2.26-2.33 (m, 2H), 2.55 (d, 3H), 2.60-2.65 (m, 2H), 2.76-2.83 (m, 1H), 2.88-2.97 (m, 1H), 3.44-3.48 (m, 1H), 4.35-4.43 (m, 1H), 6.94 (d, 2H), 7.03 (d, 2H), 7.11-7.23 (m, 3H), 7.30-7.35 (m, 1H), 7.97 (d, 1H), 8.03 (brs, 2H), 8.40 (d, 1H).	372

17	CH_3		F	H	H	2.25-2.35 (m, 2H), 2.56 (d, 3H), 2.60-2.70 (m, 2H), 2.81-2.88 (m, 1H), 2.2-2.98 (m, 1H), 3.44-3.51 (m, 1H), 4.38-4.46 (m, 1H), 6.98-7.01 (m, 1H), 7.11-7.25 (m, 6H), 7.28-7.34 (m, 1H), 8.02 (brs, 1H), 8.46 (d, 1H).	394
18	CH_3		F	F	H	2.30-2.46 (m, 2H), 2.58 (d, 3H), 2.66-2.84 (m, 2H), 2.94-3.10 (m, 2H), 3.41-3.48 (m, 1H), 4.40-4.46 (m, 1H), 7.02 (t, 1H), 7.10 (t, 1H), 7.17-7.28 (m, 6H), 7.80 (brs, 2H), 7.96-7.98 (m, 1H), 8.42-8.45 (m, 1H).	376
19	CH_3		F	H	F	2.30-2.42 (m, 2H), 2.55 (d, 3H), 2.59-2.72 (m, 2H), 2.80-2.87 (m, 1H), 2.93-3.07 (m, 2H), 4.38-4.46 (m, 1H), 7.06-7.24 (m, 8H), 7.99 (d, 1H), 8.07 brs, 2H), 8.46 (d, 1H).	376

Examples 20-30

The following examples were made as their hydrochloride salts by an analogous method to Example 11 from **Intermediate 8** and the starting materials indicated below.

Example 20: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-3-yl-ethyl)-butyramide

Starting material – see Intermediate 9

Example 21: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-4-yl-ethyl)-butyramide

Starting material – see Intermediate 10

Example 22: (R)-3-Amino-*N*-[(R)-2-(4-bromo-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide

Starting material – see Intermediate 11

Example 23: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-thiophen-3-yl-ethyl)-butyramide

Starting material – see Intermediate 12

Example 24: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-3-phenyl-propyl)-butyramide

Starting material – see Intermediate 13

Example 25: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-2-(4-methoxy-phenyl)-1-methylcarbamoyl-ethyl]-butyramide

Starting material – see Intermediate 14

Example 26: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-1-methylcarbamoyl-2-(3-trifluoromethyl-phenyl)-ethyl]-butyramide

Starting material – see Intermediate 15

Example 27: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-thiazol-4-yl-ethyl)-butyramide

Starting material – see Intermediate 16

Example 28: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-(1-methylcarbamoyl-2-quinolin-4-yl-ethyl)-butyramide

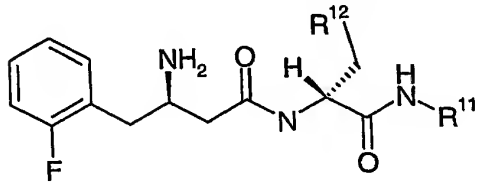
Starting material – 2-Amino-*N*-methyl-3-quinolin-4-yl-propionamide

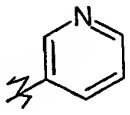
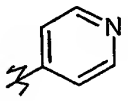
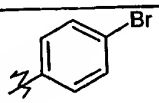
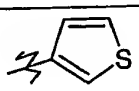
Example 29: (3*R*)-3-amino-4-(2-fluorophenyl)-*N*-[(1*R*)-2-(methylamino)-1-(1-napthylmethyl)-2-oxoethyl]butanamide

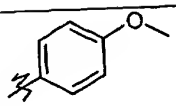
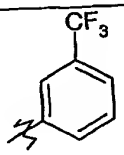
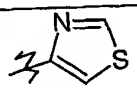
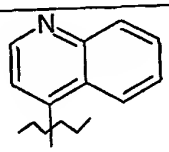
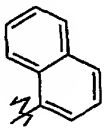
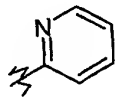
Starting material – (R)-2-Amino-*N*-methyl-3-naphthalen-1-yl-propionamide

Example 30: (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-2-yl-ethyl)-butyramide

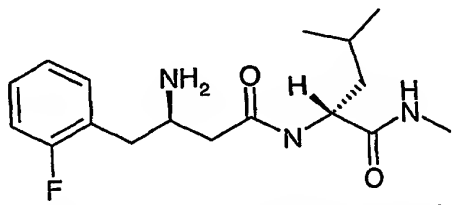
Starting material – (R)-2-Amino-*N*-methyl-3-pyridin-2-yl-propionamide



Example	R^{11}	R^{12}	^{1}H NMR (DMSO)	MS m/z
20	CH_3		2.25-2.63 (m, 2H), 2.58 (d, 3H),2.65-2.8 (dd, 1H),2.9-3.05 (m, 2H), 3.2-3.35 (dd, 1H), 3.55 (b, 1H), 4.55 (m, 1H), 7.1-7.2 (m, 2H),7.25-7.38 (m, 2H), 7.95 (dd, 1H) 8.25(b, 4H), 8.45(d, 1H), 8.65(d, 1H), 8.75(d, 1H), 8.85(s, 1H)	359
21	CH_3		225-2.5(m, 2H), 2.53(d, 3H), 2.66-2.8(dd, 1H), 2.9-3.05(m, 2H), 3.2-3.35(dd, 1H), 3.55(b, 1H), 4.58(m, 1H), 7.1-7.38(m, 4H), 7.82(d, 2H), 8.2(bs, 4H), 8.65(d, 1H), 8.73(d, 2H)	359
22	CH_3		2.25-2.58(m, 2H), 2.59(d, 3H), 2.6-2.7(m, 2H), 2.8-3.0(m, 2H), 3.5(b, 1H), 4.4(m, 1H), 7.1-7.4(m, 8H), 8.05(d, 1H), 8.13(bs, 3H), 8.5(d, 1H)	436/438
23	CH_3		2.25-2.45(m, 2H), 2.58(d, 3H), 2.7-2.82(m, 2H), 2.9-3.05(m, 2H)3.55(m, 1H) 4.4(m, 1H), 6.92(d, 1H), 7.1-7.39(m, 7H), 8.0(d, 1H), 8.15(bs, 3H), 8.45(d, 1H)	364
24	CH_3	$-CH_2Ph$	1.65-1.95(m, 2H), 2.4-2.65(m, 4H), 2.56(d, 3H), 2.8-3.1(m, 2H), 3.68(m, 1H), 4.15(m, IH), 7.1-7.4(m, 9H), 7.9(d, 1H), 8.22(bs, 3H), 8.4(d, 1H)	372

25	CH_3		2.26-2.53(m, 2H), 2.58(d, 3H), 2.6-2.7(m, 2H), 2.8-2.98(m, 2H), 3.5(m, 1H), 4.38(m, 1H), 6.7(d, 2H), 7.05-7.38(m, 6H), 8.0(d, 1H), 8.15(bs, 3H), 8.45(d, 1H)	388
26	CH_3		2.22-2.38(m, 1H), 2.4-2.68(d, 5H), 2.7-2.9(m, 2H), 3.0-3.15(m, 1H)3.5(b, 1H), 4.45(m, 1H), 7.05-7.6(m, 8 H), 8.1(b, 4H), 8.55(d, 1H)	426
27	CH_3		2.38-2.58(m, 5H), 2.75-3.22(m, 4H), 3.6(b, 1H), 4.55(m, 1H), 7.1-7.4(m, 5H), 7.95(d, 1H), 8.15(b, 3H), 8.5(d, 1H), 9.08(s, IH)	365
28	CH_3			409
29	CH_3		2.27-2.34 (m, 2H), 2.54 (d, 3H), 2.81-2.86 (m, 2H), 3.06-3.15 (m, 2H), 3.63-3.67 (m, 1H), 4.53-4.58 (m, 1H), 7.12-7.18 (m, 4H), 7.28-7.30 (m, 3H), 7.46-7.49 (m, 2H), 7.68-7.71 (m, 1H), 7.82-7.85 (m, 1H), 7.96-8.01 (m, 2H), 8.13-8.15 (m, 1H), 8.53 (d, 1H).	408
30	CH_3		2.34 (m, 1H), 2.58 (m, 3H), 2.68 - 3.04 (m, 2H), 3.41 - 3.64 (m, 3H), 4.73 (m, 1H), 7.10 - 7.22 (m, 2H), 7.23 - 7.38 (m, 2H), 7.83 (m, 2H), 8.09 - 8.59 (m, 5H), 8.65 - 8.82 (m, 2H)	359

Example 31: (S)-2-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-4-methyl-pentanoic acid methylamide

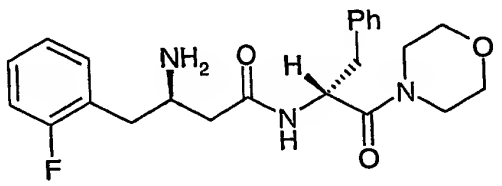


This Example was prepared as the hydrochloride salt by an analogous method to Example 11 using **Intermediate 8** and L-Leucine-N-methylamide (CAS no. 64569-68-2). The latter could

be made using the procedure as described by R.W. Feenstra *et al.*, Tetrahedron **1990**, *46*(5), 1745-56.

MS m/z 324 (MH^+).

Example 32: (R)-3-Amino-*N*-((S)-1-benzyl-2-morpholin-4-yl-2-oxo-ethyl)-4-(2-fluoro-phenyl)-butyramide



This Example was prepared as the hydrochloride salt by an analogous method to Example 11 using **Intermediate 8** and (S)-2-Amino-1-morpholin-4-yl-3-phenylpropan-1-one, hydrochloride. This amine could be made by an analogous procedure to that used to synthesise the enantiomer (CAS no. 17186-57-1) in WO9528416.

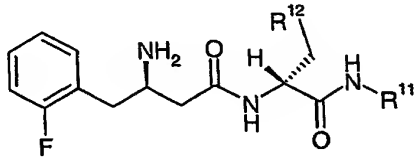
MS m/z 414 (MH^+).

Example 34 : (R)-3-Amino-*N*-(1-carbamoyl-2-furan-2-yl-ethyl)-4-(2-fluoro-phenyl)-butyramide

To a stirred solution of **Intermediate 17** (266mg, 1.3mmol) in DCM (10ml) was added (R)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid (386 mg, 1.3mmol), HOBT (199mg, 1.3mmol), EDCI (249mg, 1.3mmol), and DIPEA (0.45 ml, 2.6mmol). The mixture was stirred at RT for 16 hours to produce a white precipitate which was isolated by filtration and washed with DCM and water. The solid was then dried *in vacuo* to give 190mg of a colourless solid. This solid was stirred with dioxane /HCl for 2 hours at RT. After evaporation the residue was triturated with ether and filtered to give a solid (120mg); ^{1}H NMR (DMSO-d6) δ: 2.3-2.55(m, 2H), 2.7-3.1(m, 4H), 3.6(b, 1H), 4.45(m, 1H), 6.02-6.38(dd, 2H), (7.05-7.55(m, 7H)8.15(bs, 3H), 8.02(t, 1H); MS m/z 334 (MH^+).

Examples 33, 35 and 36

The following examples were made as their hydrochloride salts by an analogous method to Example 12 using **Intermediate 8** and the commercially available amino acid starting materials indicated below.



Example 33 : (R)-3-Amino-*N*-((R)-2-benzo[*b*]thiophen-3-yl-1-carbamoyl-ethyl)-4-(2-fluoro-phenyl)-butyramide

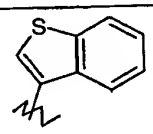
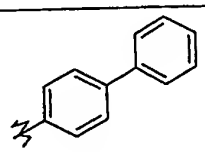
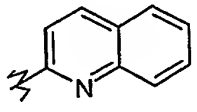
Starting material – 3-benzothienyl-D-alanine

Example 35 : (R)-3-Amino-*N*-((R)-2-biphenyl-4-yl-1-carbamoyl-ethyl)-4-(2-fluoro-phenyl)-butyramide

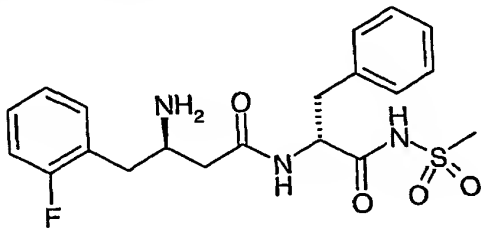
Starting material – 4-biphenyl-D-alanine

Example 36 : (R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-quinolin-2-yl-ethyl)-butyramide

Starting material – 2-quinolyl-D-alanine

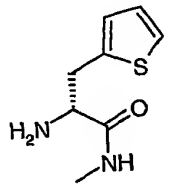
Example	R^{11}	R^{12}	^{1}H NMR (DMSO) δ:	MS m/z
33	H		2.3-2.6(m, 2H), 2.64-3.3(m, 4H), 3.5(b, 1H), 4.55(m, 1H), 7.05-7.48(m, 8H), 7.6(bs, 1H), 7.9(m, 2H), 8.15(bs, 3H), 8.53(d, 1H)	399
35	H		2.05-2.9(m, 5H), 3.0-3.1(dd, 1H), 3.5(b, 1H), 4.5(m, 1H), 7.02-7.6(m, 15H), 8.05(bs, 3H), 8.45(d, 1H)	420
36	CH_3		2.3-2.6(m, 2H), 2.73(d, 3H), 2.8-3.8(m, 5H), 4.9(m, 1H), 7.03-8.35(m, 13H), 8.75(d, 1H), 8.85(bs, 1H)	409

Example 37: (R)-3-Amino-*N*-((R)-1-benzyl-2-methanesulfonylamino-2-oxo-ethyl)-4-(2-fluoro-phenyl)-butyramide, hydrogen chloride salt



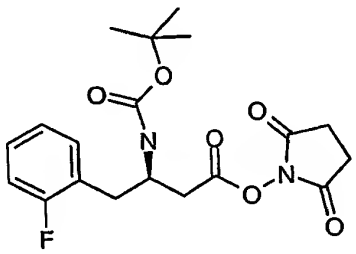
Intermediate 18 (58mg, 0.11mmol) was stirred with a 4M solution of HCl in dioxane at room temperature for 16 hours. The mixture was concentrated under reduced pressure and reconcentrated twice from ether to give the title product as a colourless solid. ^{1}H NMR (300 MHz, DMSO) δ: 2.36 - 2.45 (m, 1H), 2.60 - 3.08 (m, 4H), 3.16 (d, 2H), 3.43 - 3.51 (m, 1H), 4.53 (m, 1H), 7.06 - 7.39 (m, 10H), 8.11 (s, 3H), 8.61 (t, 1H); MS m/z 422 $(MH)^+$.

Intermediate 7: (R)-2-Amino-*N*-methyl-3-thiophen-2-yl-propionamide hydrochloride salt

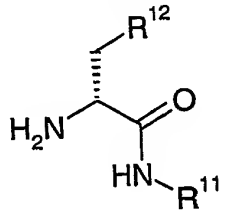


(R)-2-*tert*-Butoxycarbonylamino-3-thiophen-2-yl-propionic acid (542mg, 2mmol) was stirred with methylamine, hydrochloride (148.5mg, 2.2mmol), HOBT (337mg, 2.2mmol), EDCI (421.8mg, 2.2mmol), and DIPEA (0.77ml, 2.2mmol) in DCM (20ml) for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic extract was washed sequentially with water, 1.0N citric acid, water and brine. After drying over magnesium sulphate,the mixture was filtered and evaporated to leave a solid (450mg).This solid was stirred with 4N HCl/dioxane (20ml) at RT for 16 hours. The solvent was evaporated off and the residue was triturated with v/v ethyl acetate/isohexane to give the title compound as a white solid (300mg, 68%) MS m/z 185 (MH+).

Intermediate 8: (R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid 2,5-dioxo-pyrrolidin-1-yl ester



A mixture of (*R*)-3-Boc-Amino-4-(2'-Fluorophenyl)-Butyric Acid (10.0 g, 33.8 mmol) and N-hydroxysuccinimide (4.09 g, 35.5 mmol) in DCM (125 ml) was treated with EDAC (7.78 g, 40.6 mmol). The mixture was stirred overnight at room temperature. The mixture was diluted with DCM and washed successively with 1M HCl and aqueous sodium bicarbonate. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting solid was purified by by MPLC on silica (Isco Companion®; gradient elution from 100% DCM to 20% ethyl acetate/DCM) to give (R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid 2,5-dioxo-pyrrolidin-1-yl ester as a colourless solid (7.28g, 55%) ^1H NMR ($CDCl_3$) 1.380 (s, 9H), 2.85 (s, 6H), 2.92-3.12 (m, 2H), 4.22-4.38 (m, 1H), 4.90-5.08 (m, 1H), 6.99-7.13 (m, 2H), 7.18-7.30 (m, 2H); MS m/z 417 $(M+Na)^+$.



Intermediates 9-17 were made as their hydrochloride salts following the procedure for **Intermediate 7**, using the appropriate commercially available *N-tert*-butoxycarbonyl α-amino acids.

Intermediate 9: (R)-2-Amino-*N*-methyl-3-pyridin-3-yl-propionamide

Intermediate 10: (R)-2-Amino-*N*-methyl-3-pyridin-4-yl-propionamide

Intermediate 11: (R)-2-Amino-3-(4-bromo-phenyl)-*N*-methyl-propionamide

Intermediate 12: (R)-2-Amino-*N*-methyl-3-thiophen-3-yl-propionamide

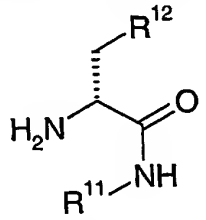
Intermediate 13: (R)-2-Amino-*N*-methyl-4-phenyl-butyramide

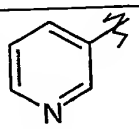
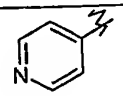
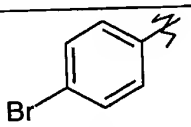
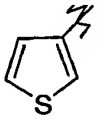
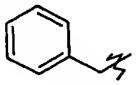
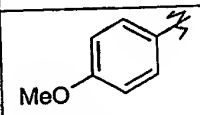
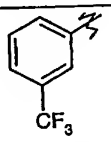
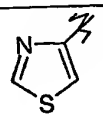
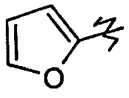
Intermediate 14: (R)-2-Amino-3-(4-methoxy-phenyl)-*N*-methyl-propionamide

Intermediate 15: (R)-2-Amino-*N*-methyl-3-(3-trifluoromethyl-phenyl) propionamide

Intermediate 16: (R)-2-Amino-*N*-methyl-3-thiazol-4-yl-propionamide

Intermediate 17: (R)-2-Amino-3-furan-2-yl-propionamide



Intermediate	R^{12}	R^{11}	MS: M+
9		CH_3	180
10		CH_3	180
11		CH_3	257/259
12		CH_3	185
13		CH_3	193
14		CH_3	209
15		CH_3	247
16		CH_3	186
17		CH_3	169

(R)-2-Amino-*N*-methyl-3-quinolin-4-yl-propionamide

(R)-2-Amino-*N*-methyl-3-quinolin-4-yl-propionamide was made as its hydrochloride salt following the procedure for **Intermediate 7** from (R)-2-*tert*-Butoxycarbonylamino-3-quinolin-4-yl-propionic acid. Obtained as a yellow hygroscopic solid; MS m/z 230 $(MH)^+$.

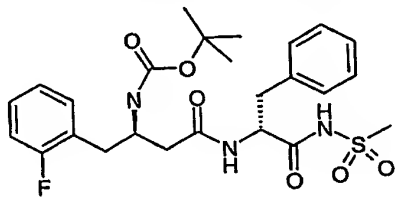
(R)-2-Amino-*N*-methyl-3-naphthalen-1-yl-propionamide

(R)-2-Amino-*N*-methyl-3-naphthalen-1-yl-propionamide was made as its hydrochloride salt following the procedure for **Intermediate 7** from (R)-2-*tert*-Butoxycarbonylamino-3-naphthalen-1-yl-propionic acid. Obtained as a colourless foam; MS m/z 251 $(M+Na)^+$, 229 $(MH)^+$.

(R)-2-Amino-N-methyl-3-pyridin-2-yl-propionamide

(R)-2-Amino-N-methyl-3-pyridin-2-yl-propionamide was made from (R)-2-*tert*-Butoxycarbonylamino-3-pyridin-2-yl-propionic acid as its TFA salt. The procedure which was used was the same as that used for **Intermediate 7** except a 2:1 mixture of DCM:TFA was used in place of the 4M HCl/dioxan in the deprotection step. A brown oil was obtained; MS m/z 202 $(M+Na)^+$, 180 $(MH)^+$.

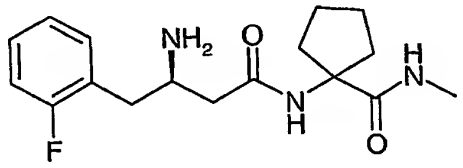
Intermediate 18: [(R)-1-[((R)-1-Benzyl-2-methanesulfonylamino-2-oxo-ethylcarbamoyl)-methyl]-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester



To a stirred solution of **Intermediate 5** (200 mg, 0.45mmol) in DCM (5ml) was added DMAP (489mg, 1.8mmol), methanesulfonamide (51mg, and 0.54mmol), and EDCI (331mg, 0.54mmol). The mixture was stirred at RT for 16 hours, evaporated, and the residue was partitioned between DCM and 1M hydrochloric acid. The organic extract was evaporated to to dryness. The residue was purified by MPLC on silica (Isco Companion®; eluting with 5% MeOH/DCM) to give a gum. The gum was further purified on an Isolute® RNH_2 column washing with 20% methanol/DCM and eluting with 5% acetic acid : 10% methanol : 85% DCM. The title product was obtained as a colourless solid (58mg, 25%) after reconcentration from ether. ^1H NMR (300 MHz, DMSO) δ: 1.13 (s, 9H), 2.13 - 2.33 (m, 2H), 2.53 (s, 1H),

2.67 - 2.85 (m, 2H), 2.92 - 3.10 (m, 4H), 3.92 (s, 1H), 4.44 (m, 1H), 6.57 (t, 1H), 6.96 - 7.29 (m, 9H), 8.02 (m, 1H), 12.07 (s, 1H); MS m/z 544 $(M+Na)^+$, 522 $(MH)^+$.

Example 38: 1-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-methylcyclopentane carboxamide hydrochloride salt



A solution of *tert*-butyl [(1*R*)-1-(2-fluorobenzyl)-3-({1-[(methylamino)carbonyl]cyclopentyl}amino)-3-oxopropyl]carbamate (**Intermediate 19,** 0.142 g, 0.337 mmol) in 4N HCl in dioxane was stirred at room temperature for 1hour. The title compound was isolated after evaporation under vacuum and trituration with ether (131 mg 100%). ^{1}H NMR (DMSO d6): 1.56 (m, 4H), 1.66-1.99 (m, 4H), 2.47-2.52 (m, 2H), 2.50 (s, 3H), 2.79-2.86 (m, 1H), 2.97-3.03 (m, 1H), 3.61-3.68 (m, 1H), 7.15-7.21 (m, 2H), 7.29-7.35 (m, 2H), 7.52-7.54 (m, 1H), 8.13 (brs, 2H), 8.25 (s, 1H); MS m/z 322 (MH+).

Intermediate 21: Methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopentanecarboxylate

To a solution of (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid (0.813 g, 2.80 mmol) in DCM (30 ml) was added Polymer supported-Carbodiimide (4.38 g, 5.60 mmol), Polystyrene diisopropylaminomethyl (2.2 g, 8.40 mmol), HOBt (0.56 g, 4.20 mmol) and methyl 1-aminocyclopentanecarboxylate hydrogen chloride (0.50 g, 2.80 mmol). The reaction mixture was allowed to stir at ambient temperature for 18 hrs, filtered and the filtrate washed with sodium hydrogen carbonate (100 ml), dried ($MgSO_4$) and concentrated. The residue was purified on a 40g Biotage silica cartridge and eluting EtOAc-isohexane (8-2) to obtain the title compound (1.0 g, 85%). ^{1}H NMR ($CDCl_3$): 1.37 s, 9H), 1.77-1.80 (m, 4H), 1.89-1.99 (m, 2H), 2.22-2.48 (m, 4H), 2.92 (d, 2H), 3.73 (s, 3H), 4.05-4.14 (m, 1H), 5.42 (brs, 1H), 6.13 (brs, 1H), 6.98-7.09 (m, 2H), 7.17-7.28 (m, 2H) ; MS m/z 445 (M+Na).

Intermediate 20: 1-{[(3*R*)-3-[(*tert*-butoxylcarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopentanecarboxylic acid

To a solution of methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopentanecarboxylate (**Intermediate 21,** 1.0g, 2.36 mmol) in THF (36 ml) and water (10 ml) was added a solution of lithium hydroxide monohydrate (0.19g, 4.74 mmol) in water (4.7 ml). The reaction mixture was allowed to stir at ambient temperature for 18 hrs, volatile material was removed by evaporation and the residue acidified to pH 2 with 1N potassium hydrogen sulphate. The aqueous solution was extracted into EtOAc (2 x 150 ml) and the organic extracts combined, dried ($MgSO_4$) and concentrated to leave the title compound (0.873 g, 91%). ^{1}H NMR (DMSO d6): 1.25 (s, 9H), 1.61 (m, 4H), 1.79-1.85 (m, 2H), 1.93-2.05 (m, 2H), 2.22 (d, 2H), 2.57-2.64 (m, 1H), 2.78-2.84 (m, 1H), 3.95-3.97 (m, 1H), 6.58 (d, 1H), 7.06 (t, 2H), 7.19-7.23 (m, 2H), 8.06 (s, 1H), 12.03 (s, 1H); MS m/z 431 (M+Na).

Intermediate 19: *tert*-Butyl [(1*R*)-1-(2-fluorobenzyl)-3-({1-[(methylamino)carbonyl]cyclopentyl}amino)-3-oxopropyl]carbamate

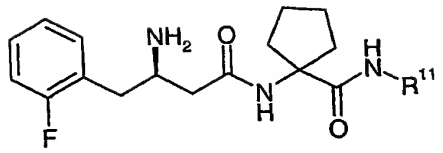
Prepared from 1-{[(3*R*)-3-[(*tert*-butoxylcarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopentanecarboxylic acid (**Intermediate 20,** 0.218 g, 0.534 mmol) and methylamine hydrochloride (37.2 mgs, 0.513 mmol) using the procedure described in **Intermediate 21** to provide the title compound (0.142 g, 63%). ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 1.68-1.77 (m, 4H), 1.90-1.98 (m, 2H), 2.21-2.51 (m, 2H), 2.41-2.51 (m, 2H), 2.79 (d, 3H), 2.91 (d, 2H), 4.05-4.15 (m, 1H), 5.24 (d, 1H), 6.06 (s, 1H), 6.87 (brs, 1H), 7.00-7.11 (m, 2H), 7.21-7.23 (m, 2H); MS m/z 578 (M+Na).

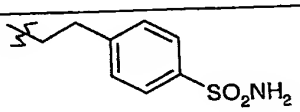
Example 39: 1-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-benzylcyclopentanecarboxamide

Example 40: 1-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[(propylsulfonyl)amino]ethyl}cyclopentanecarboxamide

Example 41: 1-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}cyclopentanecarboxamide

Example 39, 40 and 41 were made following the procedure described for **Example 38**, from **Intermediates 22, 23 and 24** respectively.



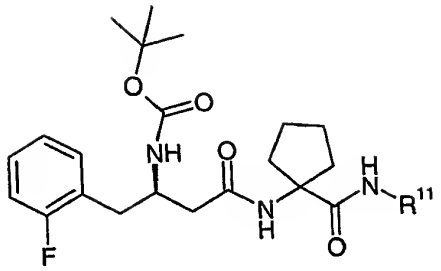
Eg	R^{11}	^{1}H NMR (DMSO)	MS m/z
39	-CH_2Ph	1.59 (m, 4H), 1.75-2.13 (m, 4H), 2.78-2.86 (m, 1H), 2.94-3.01 (m, 1H), 3.28-3.35 (m, 2H), 3.61-3.69 (m, 1H), 4.21 (t, 1H), 7.09-7.35 (m, 9H), 8.08 (brs, 2H), 8.17 (t, 1H), 8.32 (s,1H).	398 $(MH)^+$
40	-$(CH_2)_2NHSO_2Pr$	0.93 (t, 3H), 1.56-1.81 (m, 8H), 1.88-2.03 (m, 2H), 2.83-3.09 (m, 8H), 3.25-3.31 (m, 2H), 3.61-3.65 (m, 1H), 6.95 (t, 1H), 7.14-7.21 (m, 2H), 7.30-7.35 (m, 2H), 7.69 (t, 1H), 8.10 (brs, 2H), 8.34 (s, 1H),	457 $(MH)^+$
41		1.56 (m, 4H), 1.67-2.00 (m, 4H), 2.72 (t, 2H), 2.81-2.89 (m, 1H), 2.97-3.04 (m, 1H), 3.53-3.68 (m, 3H), 7.15-7.21 (m, 2H), 7.26-7.36 (m, 4H), 7.71 (d, 2H), 8.12 (brs, 2H), 8.25 (s, 1H).	491 $(MH)^+$

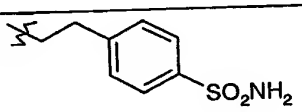
Intermediate 22: *tert*-butyl [(1*R*)-3-({1-[(benzylamino)carbonyl]cyclopentyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediate 23: *tert*-Butyl [(1*R*)-1-(2-fluorobenzyl)-3-oxo-3-({1-[({2-propylsulfonyl)amino]ethyl}amino)carbonyl]cyclopentyl}amino)propyl]carbamate

Intermediate 24: *tert*-Butyl [(1*R*)-3-({1-[({2-[4-(aminosulfonyl)phenyl]ethyl}amino) carbonyl]cyclopentyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediates 22-24 were made following the procedure described for **Intermediate 19** from **Intermediate 20** and the relevant commercially available amine (for **Intermediates 22 and 24**) or ***N*-(2-aminoethyl)propane-1-sulfonamide** (CAS No: 53673-27-1; M. S. Large and L.H. Smith, *J. Med. Chem.* **1982,** *25,* 1286.) (for **Intermediate 23**). *N*-(2-aminoethyl)propane-1-sulfonamide could be made using an analogous procedure to that used to make N-(2-Aminoethyl)methanesulfonamide in Eur. Pat. Appl., EP259092.



Inter	R^{11}	^1H NMR ($CDCl_3$)	MS m/z
22	$-CH_2Ph$	1.37 (s, 9H), 1.73-2.00 (m, 6H), 2.26-2.44 (m, 4H), 2.81 (d, 2H), 3.88-3.92 (m, 1H), 4.36-4.52 (m, 2H), 4.88 (d, 1H), 6.07 (s, 1H), 6.98-7.23 (m, 8H).	520 M+Na
23	$-(CH_2)_2NHSO_2Pr$	1.05 (t, 3H), 1.37 (s, 9H), 1.67-1.90 (m, 9H), 2.23-2.35 (m, 2H), 2.47-2.53 (m, 1H), 2.63-2.74 (m, 1H), 2.89-3.04 (m, 4H), 3.25-3.38 (m, 3H), 4.09 (m, 1H), 5.50 (brs, 1H), 5.58 (brs, 1H), 6.43 (brs, 1H), 6.69 (brs, 1H), 6.99-7.01 (m, 2H), 7.20-7.22 (m, 2H).	579 M+Na
24		(DMSO): 1.26 (s, 9H), 1.54-1.59 (m, 4H), 1.73-1.81 (m, 2H), 1.89-1.97 (m, 2H), 2.24 (d, 2H), 2.68-2.80 (m, 4H), 3.20-3.28 (m, 2H), 3.94-4.01 (m, 1H), 6.62 (d, 1H), 7.09 (t, 2H), 7.18-7.24 (m, 4H), 7.32 (d, 2H), 7.49-7.53 (m, 1H), 7.69 (d, 2H).	613 M+Na

Example 42: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid 4-fluoro-benzylamide

Example 43: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid isopropylamide

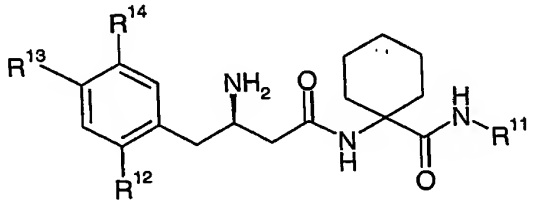
Example 44: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide

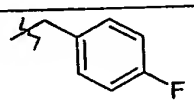
Example 45: 1-[(R)-3-Amino-4-(4-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide

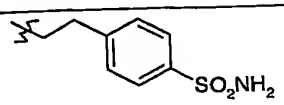
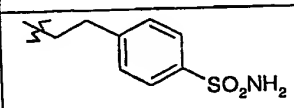
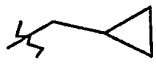
Example 46: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid cyclopropylmethyl-amide

Example 47: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-cyclohexanecarboxylic acid methylamide

Examples 42-47 were made following the same procedure as described for **Example 38** from **Intermediates 25-30** respectively.



Eg	R^{11}	R^{12}	R^{13}	R^{14}	^{1}H NMR (DMSO)	MS m/z
42		F	H	H	1.00-1.64 (m, 8H), 1.84-1.99 (dd, 2H), 2.47-2.52 (m, 2H), 2.76-2.82 (m, 1H), 2.90-2.95 (m, 1H), 3.51-3.58 (m, 1H), 4.12-4.17 (m, 2H), 6.99 (t, 2H), 7.08-7.17 (m, 4H), 7.23-7.28 (m, 2H), 7.90 (s, 1H), 8.02-8.05 (m, 3H).	429 $(MH)^+$
43	$-CH(CH_3)_2$	F	H	H	1.01 (t, 6H), 0.99-1.68 (m, 8H), 1.90-2.01 (dd, 2H), 2.56 (d, 2H), 2.88-2.97 (m, 1H), 3.00-3.04 (m, 1H), 3.61-3.66 (m, 1H), 3.77-3.81 (m, 1H), 7.17-7.24 (m, 3H), 7.33-7.39 (m, 2H), 7.81 (s, 1H), 8.15 (brs, 2H).	364 $(MH)^+$

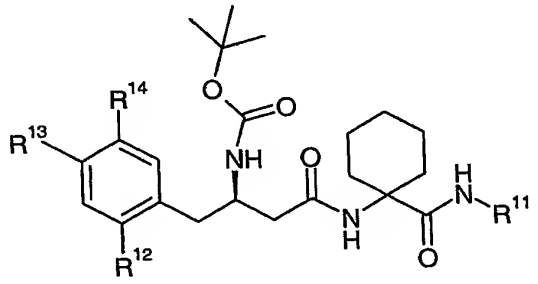
44		F	H	H	1.06-1.64 (m, 10H), 1.76-1.97 (m, 2H), 2.73 (t, 2H), 2.83-2.93 (m, 1H), 2.96-3.03 (m, 1H), 3.22-3.24 (m, 2H), 3.62-3.66 (m, 1H), 7.16-7.23 (m, 2H), 7.26 (s, 1H), 7.30-7.37 (m, 4H), 7.62-7.66 (m, 1H), 7.71 (d, 2H), 7.88 (s, 1H), 8.06 (brs, 3H).	504 $(MH)^+$
45		H	F	H	1.18-1.64 (m, 10H), 1.86-1.98 (m, 2H), 2.71-2.82 (m, 3H), 2.91-2.98 (m, 1H), 3.21-3.27 (m, 2H), 3.57-3.59 (m, 1H), 7.16 (t, 2H), 7.26-7.28 (m, 4H), 7.33 (d, 2H), 7.64 (t, 1H), 7.71 (d, 2H), 7.87 (s, 1H), 8.01 (brs, 2H).	504 $(MH)^+$
46		F	H	H	0.02-0.04 (m, 2H), 0.18-0.22 (m, 2H), 0.70-0.78 (m, 1H), 1.05-1.58 (m, 9H), 1.76-1.93 (dd, 2H), 2.44 (d, 2H), 2.76-2.94 (m, 3H), 3.49-3.54 (m, 1H), 7.02-7.12 (m, 2H), 7.22-7.28 (m, 2H), 7.40 (t, 1H), 7.77 (s, 1H), 8.02 (brs, 2H).	376 $(MH)^+$
47	CH_3	F	H	H	1.13-1.69 (m, 8H), 1.90-2.02 (dd, 2H), 2.53-2.60 (m, 5H), 2.86-2.95 (m, 1H), 3.01-3.06 (m, 1H), 3.62-3.67 (m, 1H), 7.19-7.24 (m, 2H), 7.33-7.43 (m, 2H), 7.48-7.50 (m, 1H), 7.91 (s, 1H), 8.15 (brs, 2H).	336 $(MH)^+$

Intermediates 25, 26, 29 and 30 were made from **Intermediate 47** and the relevant commercially available amine following the same procedure as described for **Intermediate 19** with the following exceptions:

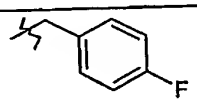
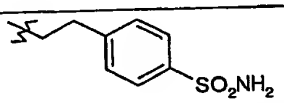
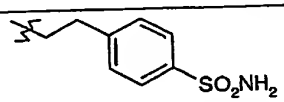
- compounds were purified by reverse phase chromatography 5-95% acetonitrile, 95-5% water, 0.2% TFA.

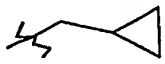
o In Intermediate 30, some deprotection occurred.

Intermediate 27& 28 were made by a similar procedure starting from 1-Amino-cyclohexanecarboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide



5

Inter	R^{11}	R^{12}	R^{13}	R^{14}	^{1}H NMR (DMSO)	MS m/z
25		F	H	H	1.19-1.26 (m, 10H), 1.43-1.62 (m, 7H), 1.91-2.07 (dd, 2H), 2.24-2.41 (m, 2H), 2.61-2.67 (m, 1H), 2.78-2.85 (m, 1H), 2.78-2.85 (m, 1H), 3.95-4.00 (m, 1H), 4.14-4.24 (m, 2H), 6.63 (d, 1H), 7.01-7.11 (m, 4H), 7.17-7.22 (m, 4H), 7.43 (s, 1H), 7.92 (t, 1H).	552 M+Na
26	-$CH(CH_3)_2$	F	H	H	0.97 (d, 6H), 1.19-1.61 (m, 17H), 2.21-2.38 (m, 2H), 2.62-2.70 (m, 1H), 2.80-2.86 (m, 1H), 3.71-3.81 (m, 1H), 3.96-4.03 (m, 1H), 6.63 (d, 1H), 6.98 (d, 1H), 7.09 (t, 2H), 7.19-7.26 (m, 3H).	486 M+Na
27		F	H	H		603 M-H
28		H	F	H		603 M-H

29		F	H	H	0.00-0.04 (m, 2H), 0.19-0.25 (m, 2H), 0.72-0.78 (m, 1H), 1.13-1.53 (m, 17H), 1.83-1.96 (m, 2H), 2.19-2.30 (m, 2H), 2.56-2.63 (m, 1H), 2.73-2.86 (m, 3H), 3.91-3.95 (m, 1H), 6.57 (d, 1H), 7.03 (t, 2H), 7.15 (t, 2H), 7.24 (t, 1H), 7.28 (s, 1H)	498 M+Na
30	$-CH_3$	F	H	H		458 M+Na

Intermediate 48: methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclohexanecarboxylate

Prepared according to the procedure described for **Intermediate 21** from (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid and methyl 1-aminocyclohexanecarboxylate (CAS No: 4507-57-7, see *Synthesis* 2002,**14**, 2023-2036) in 77% yield. ^{1}H NMR ($CDCl_3$): 1.37 (s, 9H), 1.40-1.51 (m, 6H), 1.80-2.05 (m, 4H), 2.35-2.51 (m, 2H), 2.93 (d, 2H), 3.72 (s, 3H), 4.06-4.16 (m, 1H), 5.40 (brs, 1H), 5.91)brs, 1H), 6.99-7.09 (m, 2H), 7.17-7.29 (m, 2H); MS m/z 459 (M+Na).

Intermediate 47: 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclohexanecarboxylic acid

Prepared according to the procedure described for **Intermediate 20**, from **Intermediate 48** in 83% yield. ^{1}H NMR (DMSO d_6): 1.15-1.19 (m, 1H), 1.26 (s, 9H), 1.46-1.63 (m, 7H), 1.85-1.99 (m, 2H), 2.28 (d, 2H), 2.58-2.66 (m, 1H), 2.81-2.85 (m, 1H), 3.95-3.97 (m, 1H), 6.60 (d, 1H), 7.07 (t, 2H), 7.20-7.24 (m, 2H), 7.74 (s, 1H); MS m/z 421(MH-).

1-Amino-cyclohexanecarboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide

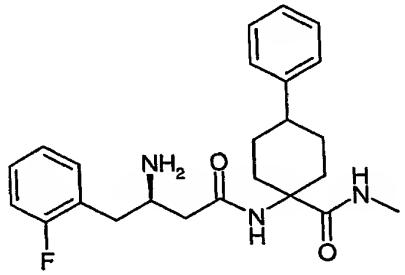
A solution of HCl in dioxan (4M, 4ml) was added to {1-[2-(4-Sulfamoyl-phenyl)-ethylcarbamoyl]-cyclohexyl}-carbamic acid *tert*-butyl ester (338mg, 0.795mmol). The mixture was stirred at room temperature for 3 hours then the solvent was evaporated to give a waxy solid which was purified by loading onto a 10g SCX cartridge, washing with methanol

and eluting with methanolic ammonia. This procedure afforded the required amine as a colourless solid (245mg, 95%). MS m/z 326 (MH^+).

{1-[2-(4-Sulfamoyl-phenyl)-ethylcarbamoyl]-cyclohexyl}-carbamic acid *tert*-butyl ester

To a stirred solution of *tert*-butoxycarbonyl-1-amino-1-cyclohexane carboxylic acid (0.243 g, 1.0mmol) in acetonitrile (5ml) was added HOBT (0.162 g, 1.2 mmol), EDCI (0.230 g, 1.2 mmol), triethylamine (0.3 ml 2.2 mmol) and 4-(2-aminoethyl)benzenesulfonamide (0.20 g, 1.0 mmol). The reaction mixture was heated in a microwave for 5 minutes. The mixture was diluted with ethyl acetate and washed with 1N aqueous potassium hydrogen sulfate (100 ml). The resulting suspension was filtered and the organic layer was washed successively with aqueous sodium bicarbonate and brine. The solution was then dried with magnesium sulphate and evaporated to give a colourless solid (0.338 g, 80%). ^{1}H NMR (DMSO d_6): 1.09 - 1.26 (m, 2H), 1.29 - 1.47 (m, 13H), 1.50 - 1.67 (m, 2H), 1.74 - 1.94 (m, 2H), 2.74 (t, 2H), 3.20 - 3.37 (m, 2H), 6.51 (s, 1H), 7.25 (s, 2H), 7.32 - 7.48 (m, 3H), 7.71 (d, 2H); MS m/z 448 (M+Na).

Example 48: 1-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-methyl-4-phenylcyclohexanecarboxamide



Example 48 was prepared from **Intermediate 35** using the procedure described in Example 38 in 74 % yield. ^{1}H NMR (DMSO d6): 1.60-1.83 (m, 7H), 2.08 (d, 1H), 2.22 (m, 1H), 2.55 (d, 3H), 2.59-2.61 (m, 2H), 2.86-2.94 (m, 1H), 3.00-3.07 (m, 1H), 3.63-3.66 (m, 1H), 7.13-7.40 (m, 8H), 7.56 (d, 1H), 8.00 (s, 1H), 8.12 (brs, 2H); MS m/z 412 (MH+).

Intermediate 31: 1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylcyclohexanecarboxylic acid

This compound was prepared according to the procedure described by Chen, Li; Cheung, Adrian Wai-hing; Chu, Xin-jie; Danho, Waleed; Swistok, Joseph; Wang, Yao; Yagaloff, Keith Alan, WO 2002018437.

Intermediate 32: Methyl 1-amino-4-phenylcyclohexanecarboxylate

Trimethylsilyldiazomethane (2M in hexanes; 2.3 ml, 4.59 mmol) was added to a solution of 1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylcyclohexanecarboxylic acid (**Intermediate 31,** 1.35 g, 3.06 mmol) in methanol (14 ml) and toluene (20 ml). The reaction mixture was allowed to stir at ambient temperature for 3 hrs and acetic acid was added and volatile material was removed by evaporation to leave methyl 1-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-4-phenylcyclohexanecarboxylate (1.29 g, 93 %) as a solid; MS m/z 456(MH^+).

This material was treated with a 20% solution of piperidine in DMF (50 ml) at ambient temperature for 2 hrs. Water (100 ml) was added and the mixture extracted into EtOAc (3 x 100 ml), the organic extracts were combined, dried ($MgSO_4$) and concentrated to leave a solid. This was purified on a 40 g silica Biotage cartridge eluting EtOAc-isohexane (1:1) to obtain the title compound (0.303 g, 46%). ^1H NMR (DMSO d6): 1.52-1.97 (m, 9H), 3.62 (s, 3H), 6.97-7.29 (m, 5H); MS m/z 234 (MH+).

Intermediate 33: Methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-4-phenylcyclohexanecarboxylate

To a stirred solution of (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid (0.386 g, 1.30mmol) in DCM (40ml) was added HOBT (0.210 g, 1.56 mmol), EDCI (0.299 g, 1.56 mmol), triethylamine (0.22 ml 1.56 mmol) and methyl 1-amino-4-phenylcyclohexanecarboxylate (**Intermediate 32,** 0.303 g, 1.3 mmol). The reaction mixture was allowed to stir at ambient temperature for 16 hours, washed with water, 1N aqueous potassium hydrogen sulfate (100 ml), sodium hydrogen carbonate (100 ml) and brine(100 ml). After drying with magnesium sulphate the solution was evaporated to leave crude product. This was purified on a 40 g silica Biotage cartridge eluting EtOAc-isohexane (1:1) to obtain the title compound (0.451 g, 68%). ^1H NMR (DMSO d6): 1.25 (s, 9H), 1.65-1.81 (m, 7H), 2.11 (d, 1H), 2.19 (d, 1H), 2.31-2.42 (m, 2H), 2.65-2.70 (m, 1H), 2.84-2.88 (m, 1H), 3.56 (s, 3H), 4.01-4.05 (m, 1H), 6.63 (d, 1H), 7.08-7.30 (m, 9H), 8.05 (s, 1H); MS m/z 535 (M+Na).

Intermediate 34: 1-{[(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-4-phenylcyclohexanecarboxylic acid

The title compound was obtained in 82% yield by hydrolysis of methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-4-phenylcyclohexanecarboxylate

(**Intermediate 33**) using the procedure described for **Intermediate 20**. ^{1}H NMR (DMSO d6): 1.22 (s, 9H), 1.52-1.77 (m, 7H), 2.11 (d, 1H), 2.22 (d, 1H), 2.32-2.39 (m, 2H), 2.63-2.70 (m, 1H), 2.82-2.89 (dd, 1H), 3.96-4.06 (m, 1H), 6.62 (d, 1H), 7.05-7.28 (m, 9H), 7.88 (s, 1H); MS m/z 521 (M+Na).

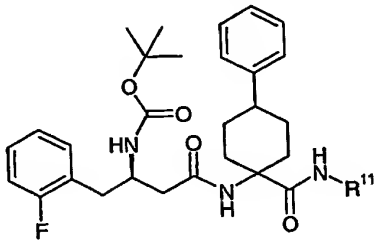
Intermediate 35: *tert*-Butyl [(1*R*)-1-(2-fluorobenzyl)-3-({1-[(methylamino)carbonyl]-4-phenylcyclohexyl}amino)-3-oxopropyl]carbamate

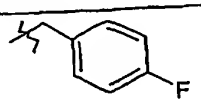
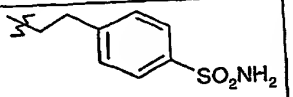
A mixture of 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}-4-phenylcyclohexanecarboxylic acid (**Intermediate 34**, 0.117 g, 0.353 mmol), HOBt (0.038 g, 0.281 mmol), EDCI (0.054 g, 0.281 mmol), triethylamine (0.06 ml, 0.498 mmol) and methylamine hydrochloride (0.018 g, 0.234 mmol) in acetonitrile (5 ml) was heated for 5 mins at 100 °C in a microwave. EtOAc (80 ml) was added and mixture was washed with 1N aqueous potassium hydrogen sulfate (50 ml), sodium hydrogen carbonate (50 ml) and brine(50 ml). After drying with magnesium sulphate the solution was evaporated to leave crude product. This was purified on a reverse phase HPLC coloumn 5-95% acetonitrile to obtain the title compound (0.100 g, 83 %). ^{1}H NMR (DMSO d6): 1.24 (s, 9H), 1.58-1.78 (m, 7H), 2.12-2.15 (m, 2H), 2.31-2.40 (m, 2H), 2.53 (d, 3H), 2.65-2.72 (m, 1H), 2.81-2.91 (m, 1H), 4.00-4.06 (m, 1H), 6.63 (d, 1H), 7.07-7.30 (m, 10H), 7.54 (s, 1H); MS m/z 534 (M+Na).

Intermediate 36: *tert*-butyl {(1*R*)-1-(2-fluorobenzyl)-3-[(1-{[(4-fluorobenzyl)amino]carbonyl}-4-phenylcyclohexyl)amino]-3-oxopropyl}carbamate

Intermediate 37: *tert*-butyl [(1*R*)-3-({1-[({2-[4-(aminosulfonyl)phenyl]ethyl}amino)carbonyl]-4-phenylcyclohexyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediates 36 and 37 were made using the procedure described for **Intermediate 35** from **Intermediate 34** and the relevant commercially available amine.

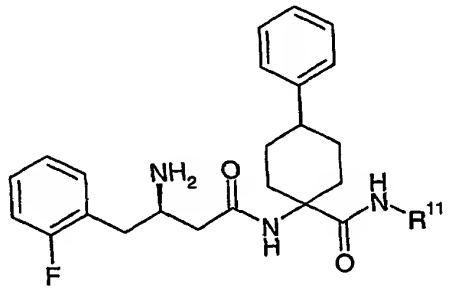


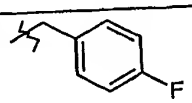
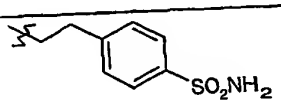
Intermediate	R^{11}	MS m/z
36		628 M+Na
37		704 M+Na

Example 49: 1-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-(4-fluorobenzyl)-4-phenylcyclohexanecarboxamide

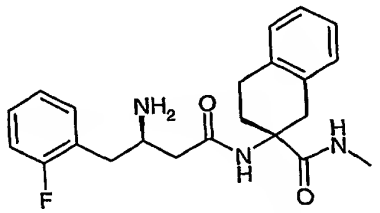
Example 50: 1-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}-4-phenylcyclohexanecarboxamide

Example 49 and 50 were made using the procedure described in Example 38, starting from **Intermediates 36 and 37** respectively:



Eg	R^{11}	^{1}H NMR (DMSO)	MS m/z
49		1.63-1.89 (m, 7H), 2.10 (d, 1H), 2.28 (d, 1H), 2.61-2.63 (m, 2H), 2.85-2.92 (dd, 1H), 2.98-3.05 (dd, 1H), 3.61-3.64 (m, 1H), 4.16-4.30 (m, 2H), 7.04-7.34 (m, 12H), 8.06 (s, 1H), 8.09 (brs, 2H), 8.19 (t, 1H).	506 $(MH)^+$
50		1.58-1.78 (m, 7H), 2.03-2.07 (m, 1H), 2.17-2.21 (m, 1H), 2.61 (d, 1H), 2.76 (t, 2H), 2.88-2.95 (dd, 2H), 3.00-3.07 (dd, 2H), 3,25-3.28 (m, 2H), 3.61-3.70 (m, 1H), 7.13-7.40 (m, 12H), 7.71 (d, 2H), 8.00 (s, 1H), 8.13 (brs, 2H).	581 $(MH)^+$

Example 51: (R)-2-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methylamide



Example 51 was prepared as described for **Example 38** from **Intermediate 49** in 98 % yield. ^{1}H NMR (DMSO d6):1.87-1.97 (m, 1H), 2.26-2.30 (m, 1H), 2.40-2.42 (m, 2H), 2.56 (d, 3H), 2.64-2.68 (m, 2H), 2.73-2.81 (m, 1H), 2.93-3.01 (m, 2H), 3.11-3.16 (m, 1H), 3.58-3.63 (m, 1H), 7.03-7.21 (m, 7H), 7.26-7.33 (m, 1H), 7.64-7.66 (m, 1H), 8.09 (brs, 2H), 8.15 (s, 1H); MS m/z 384 (MH+).

Intermediate 49: *tert*-Butyl [(1*R*)-1-(2-fluorobenzyl)-3-({(2*S*)-2-[(methylamino) carbonyl]-1,2,3,4-tetrahydronaphthalen-2-yl}amino)-3-oxopropyl]carbamate

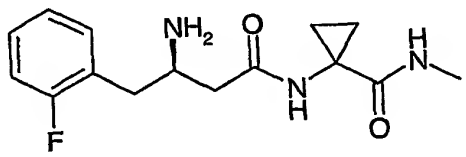
Prepared from (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid and (R)-2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methylamide according to the procedure in **Example 34** in 32% yield; MS m/z 484 (MH+).

(R)-2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methylamide

Prepared from (R)-2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid using standard procedures known to those skilled in the art (described by M. Bodansky, 'Principles of Peptide Chemistry', Springer-Verlag, New York, 1984).

(R)-2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (CAS no.104974-44-9) could be prepared according to the literature procedure (J. Aldrich, Q Zheng, T.F. Murray,. Chirality (2001), 13(3), 125-129.)

Example 52: 1-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-methylcyclopropanecarboxamide hydrogen chloride



Example 52 was prepared as described for Example 38 starting from {(R)-2-(2-Fluoro-phenyl)-1-[(1-methylcarbamoyl-cyclopropylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester. ^{1}H NMR (DMSO d6): 0.67-0.71 (m, 1H), 0.78-0.83 (m, 1H), 1.10-1.21 (m, 2H), 2.42-2.44 (m, 2H), 2.52 (d, 3H), 2.79-2.86 (m, 1H), 2.99-3.05 (m, 1H), 3.62-3.68 (m, 1H), 7.14-7.16 (m, 2H), 7.29-7.35 (m, 2H), 7.73 (d, 1H), 8.16 (brs, 2H), 8.59 (s, 1H); MS m/z 294 (MH+).

{(R)-2-(2-Fluoro-phenyl)-1-[(1-methylcarbamoyl-cyclopropylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester

Synthesised from **Intermediate 38** and methylamine according to the procedure described in **Intermediate 21**. MS m/z 417 $(M+Na)^+$.

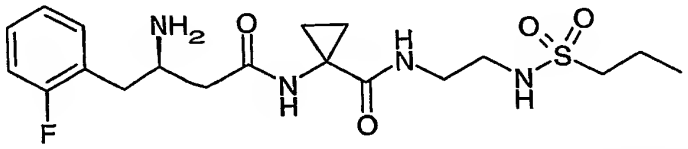
Intermediate 39: Methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopropanecarboxylate

(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid and methyl 1-aminocyclopropanecarboxylate hydrogen chloride (CAS No 72784-43-1 *JACS* 1998, 120(37), 9452-9459) were coupled together following the procedure described in **Intermediate 21** to provide the title compound in 78% yield. ^{1}H NMR ($CDCl_3$): 1.10-1.17 (m, 2H), 1.37 (s, 9H), 1.257-1.58 (m, 2H), 2.32-2.49 (m, 2H), 2.95 (d, 2H), 3.70 (s, 3H), 4.06-4.18 (m, 1H), 5.42 (brs, 1H), 6.25 (brs, 1H), 6.98-7/09 (m, 2H), 7.16-7.29 (m, 2H); MS m/z 417 (M+Na).

Intermediate 38: 1-{[(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopropanecarboxylic acid

The title compound was obtained in 92% yield by hydrolysis of methyl 1-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}cyclopropanecarboxylate (**Intermediate 39**) using the procedure described in Intermediate 20. ^{1}H NMR (DMSO d6): 0.89-0.90 (m, 2H), 0.99-1.04 (m, 1H), 1.15-1.19 (m, 1H), 1.25 (s, 9H), 2.21 (d, 2H), 2.57-2.65 (m, 1H), 2.78-2.85 (dd, 1H), 3.94-4.03 (m, 1H), 6.61 (d, 1H), 7.06 (t, 2H), 7.19-7.24 (m, 2H), 8.36 (s, 1H), 12.22 (s, 1H); MS m/z 381 (MH+).

Example 53: 1-{[(3*R*)-3-Amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[(propylsulfonyl)amino]ethyl}cyclopropanecarboxamide hydrogen chloride

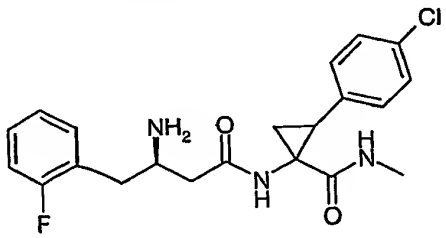


Example 53 was prepared as described for **Example 38** from **Intermediate 50** in 98 % yield. ^{1}H NMR (DMSO d6): 0.69-0.73 (m, 1H), 0.80-0.91 (m, 1H), 0.94 (t, 3H), 1.12-1.20 (m, 2H), 1.55-1.67 (m, 2H), 2.39-2.44 (m, 2H), 2.78-3.11 (m, 8H), 3.62-3.71 (m, 1H), 7.06 (t, 1H), 7.14-7.18 (m, 2H), 7.29-7.36 (m, 2H), 7.87 (t, 1H), 8.08 (brs, 2H), 8.61 (s, 1H); MS m/z 429 (MH+).

Intermediate 50: *tert*-Butyl [(1*R*)-1-(2-fluorobenzyl)-3-oxo-3-({1-[({2-[(propylsulfonyl)amino]ethyl}amino)carbonyl]cyclopropyl}amino)propyl]carbamate

Prepared according the procedure described in **Intermediate 21** from **Intermediate 38** and *N*-(2-aminoethyl)propane-1-sulfonamide (CAS No 53673-27-1 *J.Med.Chem.*, (1982), 25(11), 1286-92) in 55% yield; MS m/z 551 (M+Na).

Example 54: 1-[(R)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-2-(4-chloro-phenyl)-cyclopropanecarboxylic acid methylamide



Example 54 was made following the procedure as described for **Example 38** from **Intermediate 51** in 98% yield; MS m/z 404 (MH+).

Intermediate 51: *tert*-Butyl [(1*R*)-3-({2-(4-chlorophenyl)-1-[(methylamino)carbonyl]cyclopropyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Prepared from (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoic acid and 1-amino-2-(4-chlorophenyl)-*N*-methylcyclopropanecarboxamide (CAS No:669058-61-1 *J. Org.*

Chem., 2004, 69(4), 1262-1269) according to the procedure in **Intermediate 21** in 9% yield; MS m/z 526 (M+Na).

Example 55: (3*R*)-3-Amino-*N*-{(1*R*)-1-cyclohexyl-2-[(4-fluorobenzyl)amino]-2-oxoethyl}-4-(2-fluorophenyl)butanamide

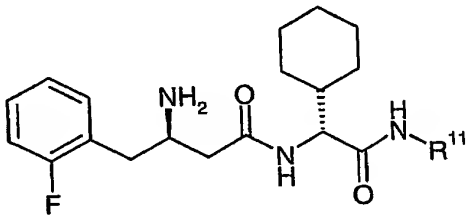
Example 56: (3*R*)-3-Amino-*N*-[(1*R*)-1-cyclohexyl-2-(isopropylamino)-2-oxoethyl]-4-(2-fluorophenyl)butanamide

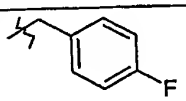
Example 57: (3*R*)-3-Amino-*N*-[(1*R*)-2-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-1-cyclohexyl-2-oxoethyl]-4-(2-fluorophenyl)butanamide

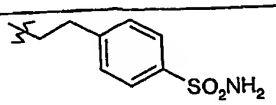
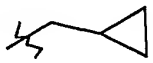
Example 58: (3*R*)-3-Amino-*N*-{(1*R*)-1-cyclohexyl-2-[(cyclopropylmethyl)amino]-2-oxoethyl}-4-(2-fluorophenyl)butanamide

Example 59: (3*R*)-3-amino-*N*-[(1*R*)-1-Cyclohexyl-2-(methylamino)-2-oxoethyl]-4-(2-fluorophenyl)butanamide

Example 55 to 59 were made using the procedure described in Example 38, starting from Intermediates 42 to 46 respectively:



Eg	R^{11}	^{1}H NMR (DMSO)	MS m/z
55		0.92-1.12 (m, 5H), 1.46-1.66 (m, 6H), 2.42-2.57 (m, 2H), 2.81-2.88 (m, 1H), 2.95-3.00 (m, 1H), 3.66 (brs, 1H), 4.12-4.17 (m, 1H), 4.23-4.26 (m, 1H), 7.08-7.40 (m, 8H), 7.96 (brs, 2H), 8.20-8.27 (m, 1H), 8.48-8.52 (m, 1H).	444 $(MH)^+$
56	$-CH(CH_3)_2$		

57		0.77-1.07 (m, 5H), 1.38-1.64 (m, 6H), 2.35-2.47 (m, 2H), 2.75-2.88 (m, 3H), 2.95-3.00 (m, 1H), 3.21-3.28 (m, 1H), 3.37-3.46 (m, 1H), 3.65 (m, 1H), 4.04-4.07 (m, 1H), 7.16-7.40 (m, 8H), 7.71 (m, 2H), 7.94 (brs, 2H), 8.09-8.20 (m, 2H).	519 $(MH)^+$
58		-0.02-0.02 (m, 2H), 0.21-0.27 (m, 2H), 0.69-1.02 (m, 6H), 1.38-1.54 (m, 6H), 2.27-2.45 (m, 2H), 2.67-2.89 (m, 4H), 3.51 (brs, 1H), 3.97 (t, 1H), 7.02-7.08 (m, 2H), 7.17-7.23 (m, 2H), 7.82 (brs, 2H), 7.91 (t, 1H), 8.02 (d, 1H).	390 $(MH)^+$
59	$-CH_3$	0.90-1.17 (m, 5H), 1.45-1.66 (m, 6H), 2.36-2.39 (m, 1H), 2.56-2.60 (m, 3H), 2.67-2.77 (m, 1H), 2.82-2.88 (m, 1H), 2.97-3.04 (m, 1H), 3.65 (brs, 1H), 4.02-4.08 (m, 1H), 7.16-7.22 (m, 2H), 7.32-7.37 (m, 2H), 7.90-7.92 (m, 1H), 8.04 (brs, 2H), 8.17-8.21 (m, 1H)	350 $(MH)^+$

Intermediate 41: methyl (2*R*)-{[(3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}(cyclohexyl)acetate

The title compound was prepared from **Intermediate 8** (1.0 g, 2.53 mmol) and methyl (2*R*)-amino(cyclohexyl)acetate hydrogen chloride (Van Boeckel, et al WO 98/07308) (0.43 g, 2.53 mmol) using the procedure described in **Example 11** (except acetonitrile was used as solvent in place of DCM) to provide the title compound (0.894 g, 79%). ^{1}H NMR (DMSO d6): 0.96-1.19 (m, 5H), 1.26 (s, 9H), 1.48-1.66 (m, 6H), 2.22-2.39 (m, 2H), 2.57-2.65 (m, 1H), 2.75-2.81 (m, 1H), 3.59 (s, 3H), 3.95-3.96 (m, 1H), 4.13 (t, 1H), 6.59 (d, 1H), 7.07 (t, 2H), 7.19 (m, 2H), 8.13 (d, 1H); MS m/z 473 (M+Na).

Intermediate 40: (2*R*)-{[(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-fluorophenyl)butanoyl]amino}(cyclohexyl)acetic acid

The title compound was obtained in 100% yield by hydrolysis of methyl (2*R*)-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}(cyclohexyl)acetate (**Intermediate 41**) using the procedure described in **Intermediate 20**. ^{1}H NMR (DMSO d6): 0.88-1.19 (m, 5H), 1.26 (s, 9H), 1.54-1.73 (m, 6H), 2.27-2.35 (m, 2H), 2.58-2.66 (m, 1H), 2.75-2.81 (m, 1H), 3.96-4.04 (m, 1H), 4.11 (t, 1H), 6.60 (d, 1H), 7.06 (t, 2H), 7.19-7.24 (m, 2H), 7.98 (d, 1H); MS m/z 459 (M+Na).

Intermediate 42: *tert*-Butyl [(1*R*)-3-({(1*R*)-1-cyclohexyl-2-[(4-fluorobenzyl)amino]-2-oxoethyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

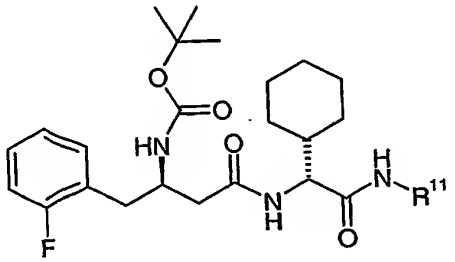
Intermediate 43: [(R)-1-{[((R)-Cyclohexyl-isopropylcarbamoyl-methyl)-carbamoyl]-methyl}-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

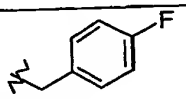
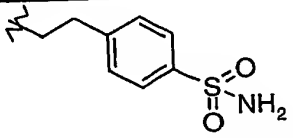
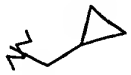
Intermediate 44: *tert*-Butyl [(1*R*)-3-{[(1*R*)-2-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-1-cyclohexyl-2-oxoethyl]amino}-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediate 45: *tert*-Butyl [(1*R*)-3-({(1*R*)-1-cyclohexyl-2-[(cyclopropylmethyl)amino]-2-oxoethyl}amino)-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediate 46: *tert*-Butyl [(1*R*)-3-{[(1*R*)-1-cyclohexyl-2-(methylamino)-2-oxoethyl]amino}-1-(2-fluorobenzyl)-3-oxopropyl]carbamate

Intermediates 42 to 46 were made using the procedure described in Intermediate 35 from Intermediate 40 and the appropriate amine, but the crude products were filtered and taken directly into the deprotection step.



Intermediate	R^{11}	MS m/z
42		566 M+Na
43	$CH(CH_3)_2$	500 M+Na
44		641 M+Na
45		512 M+Na
46	CH_3	472 M+Na

Example 60: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{2-[4-(methylsulfonyl)phenyl]ethyl}indane-2-carboxamide

Example 61 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{3-[(methylsulfonyl)amino]propyl}indane-2-carboxamide

Example 62: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{3-[(propylsulfonyl)amino]propyl}indane-2-carboxamide

Example 63: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{[1-(propylsulfonyl)piperidin-4-yl]methyl}indane-2-carboxamide

Example 64: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-{[1-(methylsulfonyl)piperidin-4-yl]methyl}indane-2-carboxamide

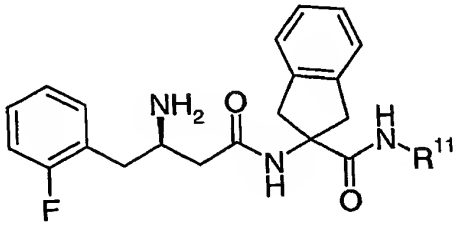
Example 65: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-[4-(methylsulfonyl)benzyl]indane-2-carboxamide

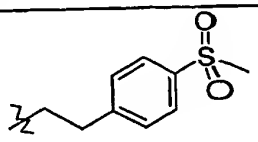
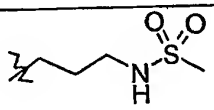
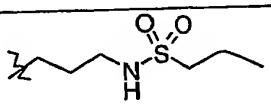
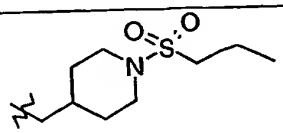
Example 66: [4-(2-{[(2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-2,3-dihydro-1*H*-inden-2-yl)carbonyl]amino}ethyl)phenoxy]acetic acid

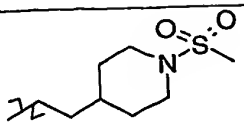
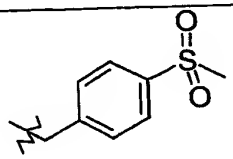
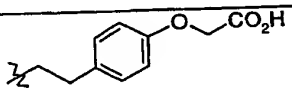
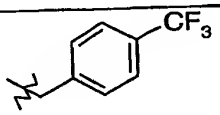
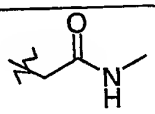
Example 67: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-[4-(trifluoromethyl)benzyl]indane-2-carboxamide

Example 68: 2-{[(3*R*)-3-amino-4-(2-fluorophenyl)butanoyl]amino}-*N*-[2-(methylamino)-2-oxoethyl]indane-2-carboxamide

Examples 60 to 68 were prepared from Intermediates 52-60 by the method described in Example 38



Example	R^{11}	^{1}H NMR (DMSO)	MS m/z
60		2.41 (d, 2H), 2.77-2.85 (m, 3H), 2.95-3.10 (m, 3H), 3.16 (s, 3H), 3.36-3.48 (m, 2H), 3.58-3.62 (m, 1H), 7.06-7.17 (m, 6H), 7.22-7.32 (m, 2H), 7.42 (d, 2H), 7.81 (d, 2H), 7.91 (t, 1H), 8.10 (brs, 2H), 8.55 (s, 1H).	538 $(MH)^+$
61		1.51-1.60 (m, 2H), 2.41-2.42 (m, 2H), 2.81-2.94 (m, 6H), 3.00-3.18 (m, 5H), 3.36-3.52 (m, 2H), 3.59-3.64 (m, 1H), 6.86 (t, 1H), 7.06-7.33 (m, 8H), 7.80 (t, 1H), 8.03 (brs, 2H), 8.57 (s, 1H).	491 $(MH)^+$
62		0.95 (t, 3H), 1.52-1.70 (m, 4H), 2.41 (d, 2H), 2.77-3.21 (m, 10H), 3.40-3.51 (m, 2H), 3.60-3.63 (m, 1H), 6.90 (t, 1H), 7.06-7.30 (m, 9H), 7.80 (t, 1H), 8.06 (brs, 2H), 8.57 (s, 1H).	491 $(MH)^+$
63		0.95 (t, 3H), 1.21-1.35 (m, 2H), 1.58-1.68 (m, 3H), 1.77-1.81 (m, 1H), 2.39 (d, 2H), 2.70-3.22 (m, 13H), 3.37-3.45 (m, 2H), 3.58-3.68 (m, 1H), 7.06-7.30 (m, 8H), 8.11 brs, 2H), 8.71 (s, 1H).	559 $(MH)^+$

64		1.21-1.34 (m, 2H), 1.63-1.81 (m, 3H), 2.38 (d, 2H), 2.80-2.84 (m, 4H), 2.86 (s, 3H), 2.95-3.22 (m, 5H), 3.35-3.51 (m, 3H), 3,58-3.66 (m, 1H), 7.03-7.31 (m, 8H), 8.08 (brs, 2H), 8.71 (s, 1H).	531 $(MH)^+$
65		2.44 (m, 2H), 2.77-2.85 (m, 1H), 2.94-3.01 (m, 1H), 3.09-3.24 (m, 2H), 3.15 (s, 3H), 3.32-3.48 (m, 2H), 3.61-3.66 (m, 1H), 4.34 (t, 2H), 7.05-7.30 (m, 8H), 7.46 (d, 2H), 7.82 (d, 2H), 8.09 (brs, 2H), 8.52 (t, 1H), 8.69 (s, 1H)	524 $(MH)^+$
66		2.38-2.41 (m, 2H), 2.59 (t, 2H), 2.70-2.81 (m, 1H), 2.94-3.20 (m, 5H), 3.33-3.49 (m, 2H), 3.59-3.63 (m, 1H), 4.60 (s, 2H), 6.70 (d, 2H), 7.04-7.32 (m, 10H), 7.82 (t, 1H), 8.04 (brs, 2H), 8.52 (s, 1H).	534 $(MH)^+$
67		2.41-2.44 (m, 2H), 2.77-2.84 (m, 1H), 2.93-3.00 (m, 1H), 3.09-3.24 (m, 2H), 3.39-3.45 (m, 2H), 3.59-3.63 (m, 1H), 4.25-4.41 (m, 2H), 7.05-7.32 (m, 8H), 7.41 (d, 2H), 7.62 (d, 2H), 8.08 (brs, 2H), 8.50 (t, 1H), 8.68 (s, 1H).	514 $(MH)^+$
68		2.41-2.43 (m, 2H), 2.57 (d, 3H), 2.79-2.99 (m, 2H), 3.01-3.17 (m, 3H), 3.48-3.67 (m, 4H), 7.08-7.31 (m, 8H), 7.41-7.42 (m, 1H), 8.08 (brs, 2H), 8.20 (t, 1H), 8.89 (s, 1H).	427 $(MH)^+$

Intermediate 52 : [(R)-2-(2-Fluoro-phenyl)-1-({2-[2-(4-methanesulfonyl-phenyl)-ethylcarbamoyl]-indan-2-ylcarbamoyl}-methyl)-ethyl]-carbamic acid *tert*-butyl ester

Intermediate 53 : ((R)-2-(2-Fluoro-phenyl)-1-{[2-(3-methanesulfonylamino-propylcarbamoyl)-indan-2-ylcarbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester

Intermediate 54 : [(R)-2-(2-Fluoro-phenyl)-1-({2-[3-(propane-1-sulfonylamino)-propylcarbamoyl]-indan-2-ylcarbamoyl}-methyl)-ethyl]-carbamic acid *tert*-butyl ester

Intermediate 55 : {(R)-2-(2-Fluoro-phenyl)-1-[(2-{[1-(propane-1-sulfonyl)-piperidin-4-ylmethyl]-carbamoyl}-indan-2-ylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester

Intermediate 56 : {(R)-2-(2-Fluoro-phenyl)-1-[(2-{2-[1-(propane-1-sulfonyl)-piperidin-4-yl]-ethylcarbamoyl}-indan-2-ylcarbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester

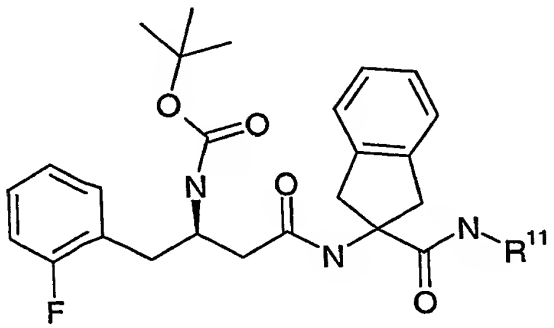
Intermediate 57 : ((R)-2-(2-Fluoro-phenyl)-1-{[2-(4-methanesulfonyl-benzylcarbamoyl)-indan-2-ylcarbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester

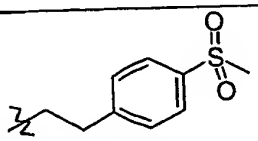
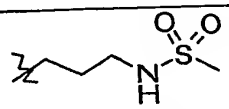
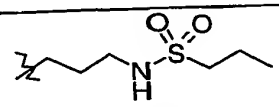
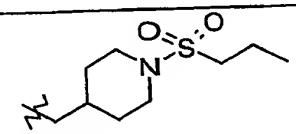
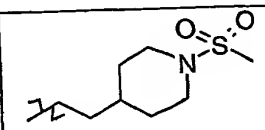
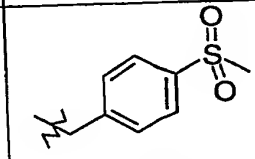
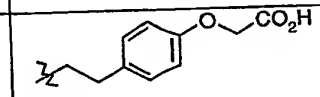
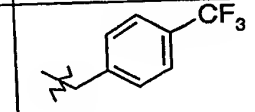
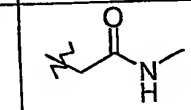
Intermediate 58 : {4-[2-({2-[(R)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-butyrylamino]-indane-2-carbonyl}-amino)-ethyl]-phenoxy}-acetic acid

Intermediate 59 : ((R)-2-(2-Fluoro-phenyl)-1-{[2-(4-trifluoromethyl-benzylcarbamoyl)-indan-2-ylcarbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester

Intermediate 60 : ((R)-2-(2-Fluoro-phenyl)-1-{[2-(methylcarbamoylmethyl-carbamoyl)-indan-2-ylcarbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester

Intermediates 52-60 were made from **Intermediate 2** and the appropriate amine starting material using the procedure described for the synthesis of **Intermediate 1**. The products were taken directly into the deprotection step.



Intermediate	R^{11}	MS m/z
52		660 (M+Na)
53		613 (M+Na)
54		613 (M+Na)
55		681 (M+Na)
56		653 (M+Na)
57		646 (M+Na)
58		656 (M+Na)
59		636 (M+Na)
60		549 (M+Na)

Intermediates used in the preparation of compounds described above were obtained as follows:-

<u>[1-(Propylsulfonyl)-piperidin-4-yl]-methylamine hydrochloride salt</u>

To a solution of piperidin-4-ylmethyl-carbamic acid *tert*-butyl ester (570 mg, 2.66 mmol) in DCM (10 ml) was added triethylamine (0.41 ml, 2.93 mmol) and 1-propanesulphonyl chloride (0.33 ml, 2.93 mmol). The reaction mixture was allowed to stir at ambient temperature for 16

hrs then washed sequentially with potassium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$) and concentrated to give a colourless gum. This residue was purified on a 40g Biotage silica cartridge and eluting EtOAc-isohexane (8-2) to obtain [1-(Propane-1-sulfonyl)-piperidin-4-ylmethyl]-carbamic acid *tert*-butyl ester (809 mg, 95 %) as a clear gum. To a portion of this gum (695 mg, 2.17 mmol) was added 4M HCl in 1,4-dioxane (5 ml) and the resulting suspension stirred for 1.5 hrs at ambient temperature. After this time the volatiles were removed to yield the title compound (770 mg, quant.) as a orange-brown solid; ^{1}H NMR (300 MHz, DMSO) δ 0.95 (t, 3H), 1.20 - 1.39 (m, 2H), 1.64 (sextet, 2H), 1.79 (d, 2H), 2.70 - 2.87 (m, 5H), 2.94 (t, 2H), 3.16 - 3.27 (m, 2H), 7.12 (t, 1H), 8.63 (s, 1H), 8.92 (s, 1H); MS m/z 220 $(M+H)^+$.

<u>*N*-(3-Aminopropyl)propane-1-sulfonamide hydrochloride salt</u>

To a solution of (3-amino-propyl)-carbamic acid *tert*-butyl ester (1.0g, 5.73 mmol) in DCM (20 ml) was added pyridine (0.51 ml, 6.31 mmol) and 1-propylsulphonyl chloride (0.71 ml, 6.31 mmol). The reaction mixture was allowed to stir at ambient temperature for 5 hrs then washed sequentially with potassium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$) and concentrated to give a yellow gum. This residue was purified on a 40g Biotage silica cartridge and eluting EtOAc-isohexane (8-2) to obtain [3-(Propane-1-sulfonylamino)-propyl]-carbamic acid *tert*-butyl ester (717 mg, 45%) as a colourless gum. To this gum was added 4M HCl in 1,4-dioxane (5 ml) and the resulting suspension stirred for 2 hrs at ambient temperature. After this time the volatiles were removed to yield the title compound (495 mg, 91 %) as a cream solid; ^{1}H NMR (300 MHz, DMSO) δ 0.96 (t, 3H), 1.58 - 1.78 (m, 4H), 2.74 - 2.85 (m, 2H), 2.92 - 3.02 (m, 4H), 7.13 (t, 1H), 7.91 (s, 3H); MS m/z 180 $(M+H)^+$.

<u>*N*-(3-aminopropyl)methanesulfonamide hydrochloride salt</u>

N-(3-aminopropyl)methanesulfonamide hydrochloride salt (CAS No: 88334-76-3) was prepared as for *N*-(3-Aminopropyl)propane-1-sulfonamide hydrochloride salt except methanesulfonyl chloride was used in place of 1-propylsulphonyl chloride; MS m/z 153 (MH^+).

[1-(methylsulfonyl)piperidin-4-yl]methylamine hydrochloride salt

[1-(methylsulfonyl)piperidin-4-yl]methylamine hydrochloride salt (CAS No 325153-03-5) was prepared as for [1-(Propylsulfonyl)-piperidin-4-yl]-methylamine hydrochloride salt except methanesulfonyl chloride was used in place of 1-propylsulphonyl chloride; MS m/z 193 (MH^+).

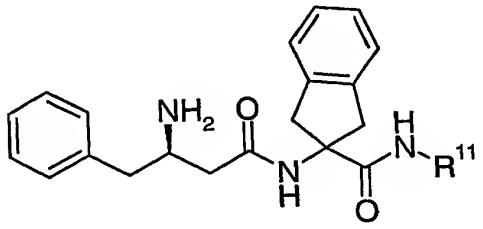
{2-[4-(Methylsulfonyl)phenyl]ethyl}amine

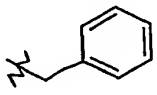
{2-[4-(Methylsulfonyl)phenyl]ethyl}amine Cas No: 153402-45-0 was prepared as described in Niu, Jinkui; Lawrence, David S. *Journal of Biological Chemistry*, 1997, **272** (3), 1493-1499.

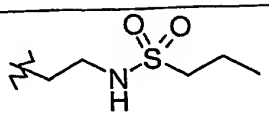
Example 69: 2-{[(3*R*)-3-amino-4-phenylbutanoyl]amino}-*N*-benzylindane-2-carboxamide

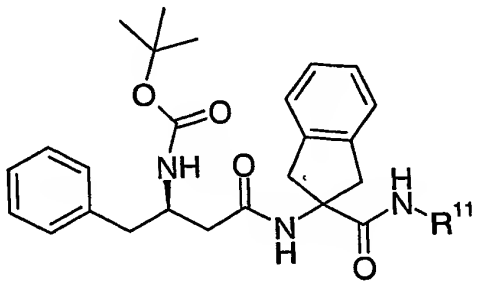
Example 70: 2-{[(3*R*)-3-amino-4-phenylbutanoyl]amino}-*N*-{2-[(propylsulfonyl)amino]ethyl}indane-2-carboxamide

Examples 69 to 70 were prepared from Intermediates 61 and 62 respectively by the method described in Example 38.



Example	R^{11}	^1H NMR (DMSO)	MS m/z
69		2.39-2.41 (m, 2H), 2.67-2.75 (m, 1H), 2.90-2.96 (m, 1H), 3.12-3.21 (m, 2H), 3.37-3.48 (m, 2H), 3.59 (m, 1H), 4.19-4.30 (m, 2H), 7.12-7.28 (m, 14H), 8.02 (brs, 2H), 8.36 (t, 1H), 8.59 (s, 1H)	428 $(MH)^+$

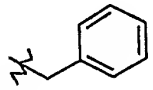
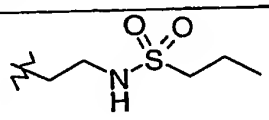
70		0.95 (t, 3H), 1.57-1.69 (m, 2H), 2.3502.40 (m, 2H), 2.68-2.75 (m, 1H), 2.90-2.95 (m, 5H), 3.04-3.22 (m, 4H), 3.39-3.60 (m, 2H), 3.59-3.62 (m, 1H), 6.95 (t, 1H), 7.15-7.26 (m, 9H), 7.89 (t, 1H), 8.00 (brs, 2H), 8.61 (s, 1H)	486 $(MH)^+$



Intermediate 61: [(R)-1-Benzyl-2-(2-benzylcarbamoyl-indan-2-ylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester

Intermediate 62: ((R)-1-Benzyl-2-{2-[2-(propane-1-sulfonylamino)-ethylcarbamoyl]-indan-2-ylcarbamoyl}-ethyl)-carbamic acid *tert*-butyl ester

Intermediates 61 and 62 were made from **Intermediate 2** and the appropriate amine using the procedure described in **Intermediate 33** and the products taken directly into the deprotection step.

Intermediate	R^{11}	MS m/z
61		550 M+Na
62		608 M+Na